TECENTRIQ® 1875mg/15ml SC

Atezolizumab
Solution for subcutaneous injection

NAME OF THE MEDICINAL PRODUCT
TECENTRIQ 1875mg/15ml SC

QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial of 15 mL solution for injection contains 1875 mg atezolizumab.
Each mL of solution contains 125 mg of atezolizumab.

Excipient with known effect
Each 1875 mg vial of TECENTRIQ 1875MG/15ML SC contains 9 mg of polysorbate 20.

For the full list of excipients, see section 11.

PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless to slightly yellowish liquid.

CLINICAL PARTICULARS

Patient safety information card and brochure
The marketing of TECENTRIQ 1875MG/15ML SC is subject to a risk management plan (RMP) including patient safety information materials (patient information card and patient brochure). These materials emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review these materials before starting treatment.

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

- TECENTRIQ 1875MG/15ML SC (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours have a PD-L1 expression ≥ 5%.
- TECENTRIQ 1875MG/15ML SC is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

1.2 Non-Small Cell Lung Cancer

- TECENTRIQ 1875MG/15ML SC, as monotherapy, is indicated as adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 50% of tumor cells (TCs).

- TECENTRIQ 1875MG/15ML SC , as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an approved test, with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ 1875MG/15ML SC, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, TECENTRIQ 1875MG/15ML SC, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated only after failure of appropriate targeted therapies.
- TECENTRIQ 1875MG/15ML SC, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ 1875MG/15ML SC is indicated for the treatment of patients with metastatic NSCLC who are naïve to anti-PD-L1 or anti-PD-1 therapies and have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ 1875MG/15ML SC.

1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ 1875MG/15ML SC, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

1.4 Small Cell Lung Cancer

TECENTRIQ 1875MG/15ML SC, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

1.5 Hepatocellular Carcinoma

TECENTRIQ 1875MG/15ML SC, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

1.6 Melanoma

TECENTRIQ 1875MG/15ML SC, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma *[see Dosage and Administration (2.1)]*.

1.7 Alveolar Soft Part Sarcoma

TECENTRIQ 1875MG/15ML SC, as a single agent, is indicated for the treatment of adult patients with unresectable or metastatic alveolar soft part sarcoma (ASPS).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Urothelial Carcinoma, Triple-Negative Breast Cancer, Non-Small Cell Lung Cancer and Melanoma

Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ 1875MG/15ML SC based on the PD-L1 expression on tumor-infiltrating immune cells *[see Clinical Studies (14.1)]*.

Select patients with Stage II to IIIA non-small cell lung cancer for treatment with TECENTRIQ 1875MG/15ML SC as a single agent based on PD-L1 expression on tumor cells *[see Clinical Studies (14.2)]*.

Select patients with first-line metastatic non-small cell lung cancer for treatment with TECENTRIQ 1875MG/15ML SC as a single agent based on the PD-L1 expression on tumor cells or on tumor infiltrating immune cells *[see Clinical Studies (14.2)]*.

Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ 1875MG/15ML SC in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells *[see Clinical Studies (14.3)]*.

Select patients with unresectable or metastatic melanoma for treatment with TECENTRIQ 1875MG/15ML SC in combination with cobimetinib and vemurafenib after confirming the presence of a BRAF V600 mutation *[see Clinical Studies (14.6)]*.

2.2 Important Dosage and Administration Information

- TECENTRIQ 1875MG/15ML SC has different recommended dosage and administration than intravenous atezolizumab products.
  - To reduce the risk of medication errors, prior to administration, check the vial labels to ensure that the drug being prepared is subcutaneously administered TECENTRIQ 1875MG/15ML SC and not intravenously administered atezolizumab.
  - Do not substitute TECENTRIQ 1875MG/15ML SC for or with intravenous atezolizumab products because they have different recommended dosages.
  - Adult patients who are treated with intravenous atezolizumab can switch to subcutaneous TECENTRIQ 1875MG/15ML SC at their next scheduled dose.
  - Adult patients who are treated with TECENTRIQ 1875MG/15ML SC can switch to intravenous atezolizumab at their next scheduled dose.
- TECENTRIQ 1875MG/15ML SC is not indicated for use in pediatric patients.
- TECENTRIQ 1875MG/15ML SC is for subcutaneous use in the thigh only. Administer over approximately 7 minutes. Inject in healthy skin and never into areas where the skin is red, bruised, tender, or hard.
- When possible, alternate injections between the left and right thigh. Ensure the injection site is at least 2.5 cm from the previous site.
- Do not administer TECENTRIQ 1875MG/15ML SC intravenously.
- TECENTRIQ 1875MG/15ML SC must be administered by a healthcare professional.
- Do **not** administer the remaining volume in the tubing to the patient.
- If using concomitant subcutaneous drugs, administer at sites other than the thighs.

2.3 Recommended Dosage and Administration Instructions

The recommended dosage of TECENTRIQ 1875MG/15ML SC is one 15 mL injection (containing 1,875 mg of atezolizumab and 30,000 units of hyaluronidase) administered subcutaneously in the thigh over approximately 7 minutes every 3 weeks.

Administration instructions for TECENTRIQ 1875MG/15ML SC as monotherapy and in combination with other therapeutic agents are presented in Table 1. For the recommended dosage of each therapeutic agent administered in combination with TECENTRIQ 1875MG/15ML SC refer to the product's respective Prescribing Information.

Table 1: TECENTRIQ 1875MG/15ML SC Administration Instructions and Duration of Therapy

Indication	**Administration Instructions for TECENTRIQ 1875MG/15ML SC**	**Duration of Therapy**
Urothelial Carcinoma	Administer TECENTRIQ 1875MG/15ML SC as monotherapy	Until disease progression or unacceptable toxicity
Adjuvant Treatment of Non-Small Cell Lung Cancer	Administer TECENTRIQ 1875MG/15ML SC as monotherapy	Up to one year, unless there is disease recurrence or unacceptable toxicity
Metastatic Non-Small Cell Lung Cancer		Until disease progression or unacceptable toxicity
Non-Small Cell Lung Cancer	Administer TECENTRIQ 1875MG/15ML SC prior to chemotherapy and bevacizumab when given on the same day.	Until disease progression or unacceptable toxicity
Locally Advanced or Metastatic Triple-Negative Breast Cancer	Administer TECENTRIQ 1875MG/15ML SC prior to paclitaxel protein-bound when given on the same day. paclitaxel protein-bound should be administered at 100 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.	
Small Cell Lung Cancer	Administer TECENTRIQ 1875MG/15ML SC prior to chemotherapy when given on the same day.	
Hepatocellular Carcinoma	Administer TECENTRIQ 1875MG/15ML SC prior to bevacizumab when given on the same day. Bevacizumab is administered intravenously at 15 mg/kg every 3 weeks.	

Melanoma	Prior to initiating TECENTRIQ 1875MG/15ML SC, patients should receive the following 28-day treatment cycle of cobimetinib and vemurafenib: • Days 1 to 21: cobimetinib 60 mg orally once daily in combination with 960 mg of oral vemurafenib twice daily • Days 22 to 28: withhold cobimetinib and administer vemurafenib 720 mg orally twice daily	
Alveolar Soft Part Sarcoma	Administer TECENTRIQ 1875MG/15ML SC as monotherapy	Until disease progression or unacceptable toxicity

2.4 Dosage Modifications for Adverse Reactions

No dose reduction for TECENTRIQ 1875MG/15ML SC is recommended.

In general, withhold TECENTRIQ 1875MG/15ML SC for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TECENTRIQ 1875MG/15ML SC for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce the daily corticosteroid dosage to 10 mg or less of prednisone or equivalent corticosteroid dosage within 12 weeks of initiating corticosteroids.

Dosage modifications for TECENTRIQ 1875MG/15ML SC for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modification**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]

Adverse Reaction	Severity[a]	Dosage Modification
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3, or 4	Withhold until clinically stable or permanently discontinue depending on severity.
Nephritis with Renal Dysfunction	Grades 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grades 1 or 2	Pause or slow the rate of injection Premedication with antipyretic and antihistamines may be considered for subsequent doses.
	Grades 3 or 4	Permanently discontinue

[a] Based on Common Terminology Criteria for Adverse Events (CTCAE) version 5

[b.] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

[c.] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson syndrome, TEN = toxic epidermal necrolysis

2.5 Preparation Instructions

TECENTRIQ 1875MG/15ML SC does not contain any antimicrobial preservative. If the TECENTRIQ 1875MG/15ML SC dose is not administered immediately, refer to "Storage Instructions" *[see Dosage and Administration (2.6)]*.

- Remove the vial from the refrigerator and allow the solution to acclimate to room temperature. Visually inspect for particulate matter and discoloration prior to administration. Discard the vial if the solution is cloudy, discolored, or visible particles are observed.
- Do not shake, freeze, or dilute.
- The unpunctured vial may be stored at room temperature in ambient light for a maximum of 4 hours prior to the preparation for administration.
- Use an 18-gauge transfer needle and syringe to withdraw the entire contents of the TECENTRIQ 1875MG/15ML SC solution from the vial. Discard the vial and any residual drug remaining.
- TECENTRIQ 1875MG/15ML SC is compatible with stainless steel transfer and injection needles, and polypropylene, polycarbonate, polyvinyl chloride, and polyurethane syringe material and subcutaneous administration sets.
- Remove the transfer needle from the syringe and replace it with a subcutaneous administration set (e.g. winged/butterfly) containing 23-gauge, 24-gauge, or 25-gauge hypodermic needle and with a priming volume that does **not** exceed 0.5 mL for administration.
- Prime the subcutaneous administration line with TECENTRIQ 1875MG/15ML SC to eliminate the air in the line and stop when the fluid reaches the needle.
- Ensure the syringe contains exactly 15 mL of TECENTRIQ 1875MG/15ML SC after priming the administration line by expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging.
- Discard any unused portion remaining.

2.6 Storage Instructions

- Do **not** store the prepared syringe that has been attached to the already-primed subcutaneous administration set.
- If the prepared syringe containing TECENTRIQ 1875MG/15ML SC is not for immediate use, do **not** attach a subcutaneous administration set. Do **not** shake or freeze. For storage conditions of the prepared syringe refer to "shelf life of the prepared syringe" *[see HOW SUPPLIED/STORAGE AND HANDLING (16)]*.
- If the prepared syringe is stored at 2°C to 8°C, allow the syringe to acclimate to room temperature prior to administration.

3. DOSAGE FORMS AND STRENGTHS

Injection: 1,875 mg atezolizumab and 30,000 units hyaluronidase per 15 mL (125 mg and 2,000 units per mL) clear, colorless to slightly yellowish liquid in a single-dose vial.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

5. WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ 1875MG/15ML SC is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity [*see Dosage Modifications for Adverse Reactions (2.4)*]. In general, if TECENTRIQ 1875MG/15ML SC requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TECENTRIQ 1875MG/15ML SC can cause immune-mediated pneumonitis, including fatal adverse reactions. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 2% (5/247) of patients with locally advanced or metastatic NSCLC receiving TECENTRIQ 1875MG/15ML SC as monotherapy in the IMscin001 trial [see Adverse Reactions (6.1)], including Grade 2 (0.8%) and Grade 1 (1.2%) events. Pneumonitis led to the withholding of TECENTRIQ 1875MG/15ML SC in one patient.

Systemic corticosteroids were required in 40% (2/5) of patients with pneumonitis who received TECENTRIQ 1875MG/15ML SC as monotherapy. Pneumonitis resolved in both patients. The single patient in whom TECENTRIQ 1875MG/15ML SC was withheld for pneumonitis, reinitiated TECENTRIQ 1875MG/15ML SC after symptom improvement.

Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib:

Immune-mediated pneumonitis occurred in 13% (29/230) of patients receiving intravenous atezolizumab in combination with cobimetinib and vemurafenib in the IMspire150 trial *[see Adverse Reactions (6.1)],* including Grade 3 (1.3%) and Grade 2 (7%) adverse reactions. Pneumonitis led to permanent discontinuation of intravenous atezolizumab in 2.6% of patients and withholding of intravenous atezolizumab in 7.4% of patients.

Systemic corticosteroids were required in 55% (16/29) of patients with pneumonitis. Pneumonitis resolved in 97% of the 29 patients. Of the 17 patients in whom intravenous atezolizumab was withheld for pneumonitis, 10 reinitiated intravenous atezolizumab after symptom improvement; of these, 50% had recurrence of pneumonitis.

Immune-Mediated Colitis

TECENTRIQ 1875MG/15ML SC can cause immune-mediated colitis, including Grade 3 adverse reactions. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis

TECENTRIQ 1875MG/15ML SC can cause immune-mediated hepatitis, including fatal adverse reactions.

Immune-mediated hepatitis occurred in 1.2% (3/247) of patients with locally advanced or metastatic NSCLC receiving TECENTRIQ 1875MG/15ML SC as monotherapy in the IMscin001 trial *[see Adverse Reactions (6.1)],* including Grade 1 (0.4%) and Grade 3 (0.8%) events. Hepatitis led to the withholding of TECENTRIQ 1875MG/15ML SC in 0.4% of patients.

Systemic corticosteroids were required in 67% (2/3) of patients with hepatitis who received TECENTRIQ 1875MG/15ML SC as monotherapy. Hepatitis resolved in 1 of the 3 patients.

Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib:

Immune-mediated hepatitis occurred in 6.1% (14/230) of patients receiving intravenous atezolizumab in combination with cobimetinib and vemurafenib in the IMspire150 trial *[see Adverse Reactions (6.1)],* including Grade 4 (1.3%), Grade 3 (1.7%) and Grade 2 (1.3%) adverse reactions. Hepatitis led to permanent discontinuation of intravenous atezolizumab in 2.2% and withholding of intravenous atezolizumab in 1.7% of patients.

Systemic corticosteroids were required in 50% (7/14) of patients with hepatitis. Hepatitis resolved in 93% of the 14 patients. Of the 4 patients in whom intravenous atezolizumab was withheld for hepatitis, 3 reinitiated intravenous atezolizumab after symptom improvement; of these, 33% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TECENTRIQ 1875MG/15ML SC can cause primary or secondary adrenal insufficiency, including Grade 3 adverse reactions. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity *[see Dosage Modifications for Adverse Reactions (2.4)]*.

Immune-mediated adrenal insufficiency occurred in 0.8% (2/247) of patients with locally advanced or metastatic NSCLC receiving TECENTRIQ 1875MG/15ML SC as monotherapy in the IMscin001 trial *[see Adverse Reactions (6.1)]*, including Grade 2 (0.4%) adverse reactions. Adrenal insufficiency led to the withholding of TECENTRIQ 1875MG/15ML SC in both patients.

Systemic corticosteroids were required in 50% (1/2) of patients with adrenal insufficiency who received TECENTRIQ 1875MG/15ML SC as monotherapy; this single patient remained on systemic corticosteroids.

Hypophysitis

TECENTRIQ 1875MG/15ML SC can cause immune-mediated hypophysitis including Grade 2 adverse reactions. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity *[see Dosage Modifications for Adverse Reactions (2.4)]*.

Immune-mediated hypophysitis occurred in <0.4% (1/247) of patients with locally advanced or metastatic NSCLC in the IMscin001 trial *[see Adverse Reactions (6.1)]* receiving TECENTRIQ 1875MG/15ML SC as monotherapy, including Grade 1 (0.4%) adverse reactions. Hypophysitis led to the withholding of TECENTRIQ 1875MG/15ML SC in this patient.

Thyroid Disorders:

TECENTRIQ 1875MG/15ML SC can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated. Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity *[see Dosage Modifications for Adverse Reactions (2.4)]*.

Thyroiditis:

Immune-mediated thyroiditis occurred in 0.8% (2/247) of patients with locally advanced or metastatic NSCLC receiving TECENTRIQ 1875MG/15ML SC as monotherapy in the IMscin001 trial *[see Adverse Reactions (6.1)]*, including Grade 2 (<0.4%) adverse reactions. Thyroiditis resolved in 50% of patients.

Hyperthyroidism:

Immune-mediated hyperthyroidism occurred in 2% (5/247) of patients with locally advanced or metastatic NSCLC receiving TECENTRIQ 1875MG/15ML SC as monotherapy in the

IMscin001 trial *[see Adverse Reactions (6.1)]*, including Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to withholding of TECENTRIQ 1875MG/15ML SC in 0.8% of patients.

Anti-thyroid therapy was required in 40% (2/5) of patients with hyperthyroidism who received TECENTRIQ 1875MG/15ML SC as monotherapy. Of these 2 patients, one remained on anti-thyroid treatment. Of the 2 patients in whom TECENTRIQ 1875MG/15ML SC was withheld for hyperthyroidism, 1 patient reinitiated TECENTRIQ 1875MG/15ML SC; this patient did not have recurrence of hyperthyroidism.

Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib:

Hyperthyroidism occurred in 19% (43/230) of patients receiving intravenous atezolizumab in combination with cobimetinib and vemurafenib in the IMspire150 trial *[see Adverse Reactions (6.1)]*, including Grade 3 (0.9%) and Grade 2 (7.8%) adverse reactions. Hyperthyroidism led to permanent discontinuation of intravenous atezolizumab in 0.4% and withholding of intravenous atezolizumab in 10% of patients.

Antithyroid therapy was required in 53% (23/43) of patients with hyperthyroidism. Of these 23 patients, the majority remained on antithyroid treatment. Of the 24 patients in whom intravenous atezolizumab was withheld for hyperthyroidism, 18 patients reinitiated intravenous atezolizumab; of these, 28% had recurrence of hyperthyroidism.

Hypothyroidism:

TECENTRIQ 1875MG/15ML SC can cause immune-mediated hypothyroidism, including Grade 4 adverse reactions. Immune-mediated hypothyroidism occurred in 10% (25/247) of patients with locally advanced or metastatic NSCLC who received TECENTRIQ 1875MG/15ML SC as monotherapy in the IMscin001 trial *[see Adverse Reactions (6.1)]*.

Hormone replacement was required in 68% (17/25) of patients with hypothyroidism who received TECENTRIQ 1875MG/15ML SC as monotherapy. Two patients with hypothyroidism remained on thyroid hormone replacement.

Intravenous Atezolizumab in Combination with Platinum-based Chemotherapy:

Hypothyroidism occurred in 11% (277/2421) of patients with NSCLC (N = 2223) or SCLC (N = 198) enrolled in five randomized, active-controlled trials, including IMpower150, IMpower130 and IMpower133 receiving intravenous atezolizumab in combination with platinum-based chemotherapy, including Grade 4 (< 0.1%), Grade 3 (0.3%), and Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of intravenous atezolizumab in 0.1% and withholding of intravenous atezolizumab in 1.6% of patients.

Hormone replacement therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom intravenous atezolizumab was withheld for hypothyroidism, 9 reinitiated intravenous atezolizumab after symptom improvement.

Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib:

Hypothyroidism occurred in 26% (60/230) of patients receiving intravenous atezolizumab in combination with cobimetinib and vemurafenib in the IMspire150 trial *[see Adverse Reactions (6.1)]*, including Grade 2 (9.1%) adverse reactions. Hypothyroidism led to withholding of intravenous atezolizumab in 2.6% of patients.

Hormone replacement therapy was required in 52% (31/60) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 6 patients in whom intravenous atezolizumab was withheld for hypothyroidism, 4 reinitiated

intravenous atezolizumab after symptom improvement. The majority of patients with hypothyroidism required long term thyroid replacement.

Type 1 Diabetes Mellitus , which can present with Diabetic Ketoacidosis

TECENTRIQ 1875MG/15ML SC can cause type 1 diabetes mellitus, including Grade 3 adverse reactions and diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity *[see Dosage Modifications for Adverse Reactions (2.4)]*.

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ 1875MG/15ML SC can cause immune-mediated nephritis, including Grade 3 adverse reactions.

Intravenous Atezolizumab in Combination with Cobimetinib and Vemurafenib:

Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving intravenous atezolizumab in combination with cobimetinib and vemurafenib in the IMspire150 trial *[see Adverse Reactions (6.1)]*, including Grade 2 (1.3%) adverse reactions. Nephritis led to permanent discontinuation of intravenous atezolizumab in 0.4% and withholding of intravenous atezolizumab in 0.9% of patients.

Systemic corticosteroids were required in 67% (2/3) of patients with nephritis. Nephritis resolved in all 3 of these patients. Of the 2 patients in whom intravenous atezolizumab was withheld for nephritis, both reinitiated intravenous atezolizumab after symptom improvement and neither had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TECENTRIQ 1875MG/15ML SC can cause immune-mediated rash or dermatitis ,including Grade 3 and fatal adverse reactions. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TECENTRIQ 1875MG/15ML SC depending on severity *[see Dosage Modifications for Adverse Reactions (2.4)]*.

One fatal case of an immune-mediated dermatologic adverse reaction, due to TEN, occurred (0.4%, 1/247) in patients with locally advanced or metastatic NSCLC receiving TECENTRIQ as monotherapy in the IMscin001 trial *[see Adverse Reactions (6.1)]*.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% (unless otherwise noted) in patients receiving intravenous atezolizumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

- *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis
- *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
- *Ocular*: Uveitis, iritis, and other ocular inflammatory toxicities occurred. Some cases were associated with retinal detachment. Various grades of visual impairment, including blindness, occurred. If uveitis occurs in combination with other immune-

mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

- *Gastrointestinal:* Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.
- *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.
- *Endocrine:* Hypoparathyroidism
- *Other (Hematologic/Immune)*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

TECENTRIQ 1875MG/15ML SC can cause severe or life-threatening infusion-related reactions, including Grade 3 adverse reactions and anaphylaxis. Monitor for signs and symptoms of infusion-related reactions. Pause, slow the rate of, or permanently discontinue TECENTRIQ 1875MG/15ML SC based on the severity *[see Dosage Modifications for Adverse Reactions (2.4)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ 1875MG/15ML SC can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ 1875MG/15ML SC in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ 1875MG/15ML SC. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ 1875MG/15ML SC and for 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Effects on ability to drive and use machines

TECENTRIQ 1875MG/15ML SC has minor influence on the ability to drive and use machines. Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 6).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions of TECENTRIQ 1875MG/15ML SC in Adult Patients with NSCLC

The safety of TECENTRIQ 1875MG/15ML SC was evaluated in IMscin001, open-label, multi-center, international, randomized trial for patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy and who have had disease progression on prior platinum-based therapy *[see Clinical Studies (14.2)]*. Patients with previously treated metastatic non-small cell lung cancer (NSCLC) either received TECENTRIQ 1875MG/15ML SC (containing 1,875 mg of atezolizumab and 30,000 units of hyaluronidase) administered subcutaneously into the thigh over approximately 7 minutes every 3 weeks or intravenous atezolizumab every 3 weeks until disease progression or unacceptable toxicity. Among 247 patients who received TECENTRIQ 1875MG/15ML SC, 32% were exposed for 6 months or longer and 8% were exposed for greater than one year.

The median age was 64 years (range: 27 to 85); 69% male; 67% White, 22% Asian, 0.8% Black or African American; 74% were non-Hispanic or Latino; 26% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 74% had an ECOG PS of 1; and 70% of patients were current or previous smokers.

Serious adverse reactions occurred in 19% of patients who received TECENTRIQ 1875MG/15ML SC. Serious adverse reactions (> 1%) included pneumonia, myocardial infarction, and pleural effusion. Fatal adverse reactions occurred in 6% of patients who received TECENTRIQ 1875MG/15ML SC, including pneumonia (2.4%), myocardial infarction (1.2%), head injury (0.4%), ischemic stroke (0.4%), pleural effusion (0.4%), pulmonary embolism (0.4%), respiratory tract infection (0.4%), sepsis (0.4%), and toxic epidermal necrolysis (0.4%).

Permanent discontinuation of TECENTRIQ 1875MG/15ML SC due to an adverse reaction occurred in 3.6% of patients. Adverse reactions which resulted in permanent discontinuation of TECENTRIQ 1875MG/15ML SC in > 1% of patients included pneumonia (2%).

Dosage interruptions of TECENTRIQ 1875MG/15ML SC due to an adverse reaction occurred in 32% of patients. Adverse reactions which required dosage interruption in > 1% of patients were

COVID-19 (4.9%), increased aspartate aminotransferase (2.8%), increased alanine aminotransferase (2.4%), pneumonia (2.4%), anemia (1.6%), dyspnea (1.6%), fatigue (1.2%), and viral respiratory tract infection (1.2%). The most common adverse reactions of any grade (occurring in ≥ 10% of patients) were fatigue (19%), musculoskeletal pain (15%), cough (13%), dyspnea (12%), and decreased appetite (11%).

Tables 3 and 4 summarize adverse reactions and selected laboratory abnormalities, respectively in TECENTRIQ 1875MG/15ML SC -treated patients in IMscin001.

Table 3: Adverse Reactions (≥ 10%) in Adult Patients with Locally Advanced or Metastatic NSCLC Who Received TECENTRIQ 1875MG/15ML SC in IMscin001

Adverse Reaction*	**TECENTRIQ 1875MG/15ML SC n = 247**		**Intravenous Atezolizumab n = 124**	
	All Grades (%)	**Grades 3–4 (%)**	**All Grades (%)**	**Grades 3–4 (%)**
General Disorder and Administration Site Conditions				
Fatigue[1]	19	0.8	18	0
Musculoskeletal and Connective Tissue disorders				
Musculoskeletal Pain[2]	15	0.4	13	3.2
Respiratory, Thoracic and Mediastinal				
Cough[3]	13	0	7	0
Dyspnea[4]	12	1.2	15	1.6
Metabolism and Nutrition Disorders				
Decreased appetite	11	0	11	0

* Graded per NCI CTCAE v5.0

[1] Composite term includes fatigue, asthenia

[2] Composite term includes back pain, myalgia, bone pain, musculoskeletal chest pain, neck pain, spinal pain, non-cardiac chest pain

[3] Composite term includes cough, productive cough

[4] Composite term includes dyspnea, dyspnea at rest, dyspnea exertional

Clinically relevant adverse reactions in < 10% of patients who received TECENTRIQ 1875MG/15ML SC were local injection site reactions (4.5%) and pyrexia (1.2%).

Table 4: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Adult Patients with Advanced or Metastatic NSCLC Who Received TECENTRIQ 1875MG/15ML SC in IMscin001

Laboratory Abnormality[1]	TECENTRIQ 1875MG/15ML SC (n = 247)		Intravenous Atezolizumab (n = 124)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Hemoglobin	67	6	63	5
Decreased lymphocytes	37	9	45	15
Chemistry				
Decreased Sodium	46	3.9	47	5
Decreased Albumin	34	2.2	27	0
Increased Alkaline Phosphatase	33	1.3	27	0
Increased AST	28	2.6	32	2.6
Increased ALT	28	2.6	23	1.7
Decreased calcium	22	2.6	23	0.9
Increased calcium	20	2.6	24	1.7
Increased potassium	21	1.7	22	1.7
Increased INR	20	2	23	0
Increased Creatinine	19	1.7	26	0.9

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ 1875MG/15ML SC (48-233) and intravenous atezolizumab (19-117)
[1] Graded per NCI CTCAE v5.0

Adverse Reactions in Adult Patients with NSCLC Treated with Intravenous Atezolizumab

The safety of TECENTRIQ 1875MG/15ML SC for its approved NSCLC indications *[see Indications and Usage (1.2)]* has been established in adequate and well-controlled studies of intravenous atezolizumab for the:

- adjuvant treatment (following tumor resection and platinum-based chemotherapy) in adult patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells (IMpower010 study).
- first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), with no EGFR or ALK genomic tumor aberrations (IMpower110 study).
- first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (IMpower150 study).
- first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (IMpower130 study).

- first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression, with no EGFR or ALK genomic tumor aberrations (OAK study).

Below is a description of adverse reactions of intravenous atezolizumab in these adequate and well-controlled NSCLC studies.

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant Treatment of Early-stage NSCLC

IMpower010

The safety of intravenous atezolizumab was evaluated in IMpower010, a multicenter, open-label, randomized trial for the adjuvant treatment of patients with stage IB (tumors ≥ 4 cm) - IIIA NSCLC who had complete tumor resection and received up to 4 cycles of cisplatin-based adjuvant chemotherapy. Patients received intravenous atezolizumab 1200 mg every 3 weeks (n=495) for 1 year (16 cycles), unless disease progression or unacceptable toxicity occurred, or best supportive care *[see Clinical Studies (14.2)]*. The median number of cycles received was 16 (range: 1, 16).

Fatal adverse reactions occurred in 1.8% of patients receiving intravenous atezolizumab; these included multiple organ dysfunction syndrome, pneumothorax, interstitial lung disease, arrhythmia, acute cardiac failure, myocarditis, cerebrovascular accident, death of unknown cause, and acute myeloid leukemia (1 patient each).

Serious adverse reactions occurred in 18% of patients receiving intravenous atezolizumab. The most frequent serious adverse reactions (>1%) were pneumonia (1.8%), pneumonitis (1.6%), and pyrexia (1.2%).

Intravenous atezolizumab was discontinued due to adverse reactions in 18% of patients*;* the most common adverse reactions (≥1%) leading to intravenous atezolizumab discontinuation were pneumonitis (2.2%), hypothyroidism (1.6%), increased aspartate aminotranferase (1.4%), arthralgia (1.0%), and increased alanine aminotransferase (1.0%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 29% of patients; the most common (>1%) were rash (3.0%), hyperthyroidism (2.8%), hypothyroidism (1.6%), increased AST (1.6%), pyrexia (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), headache (1.2%), peripheral neuropathy (1.2%), and pneumonia (1.2%).

Tables 5 and 6 summarize adverse reactions and selected laboratory abnormalities in patients receiving intravenous atezolizumab in IMpower010.

Table 5: Adverse Reactions Occurring in ≥10% of Patients with Early Stage NSCLC Receiving Intravenous Atezolizumab in IMpower010

Adverse Reaction*	Intravenous Atezolizumab N = 495		Best Supportive Care N = 495	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Skin and Subcutaneous Tissue				
Rash[1]	17	1.2	1.4	0
Pruritus	10	0	0.6	0
Endocrine Disorders				

Hypothyroidism[2]	14	0	0.6	0
Respiratory, Thoracic and Mediastinal				
Cough[3]	16	0	11	0
General				
Pyrexia[4]	14	0.8	2.2	0.2
Fatigue[5]	14	0.6	5	0.2
Nervous System Disorders				
Peripheral neuropathy[6]	12	0.4	7	0.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[7]	14	0.8	9	0.2
Arthralgia[8]	11	0.6	6	0

*Graded per NCI CTCAE v4.0

[1] Includes rash, dermatitis, genital rash, skin exfoliation, rash maculo-papular, rash erythematous, rash papular, lichen planus, eczema asteatotic, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, dyshidrotic eczema, eczema, drug eruption, rash pruritic, toxic skin eruption, dermatitis acneiform

[2] Includes hypothyroidism, autoimmune hypothyroidism, primary hypothyroidism, blood thyroid stimulating hormone increased

[3] Productive cough, upper airway cough syndrome, cough

[4] Includes pyrexia, body temperature increased, hyperthermia

[5] Includes fatigue, asthenia

[6] Includes paraesthesia, neuropathy peripheral, peripheral sensory neuropathy, hypoaesthesia, polyneuropathy, dysaesthesia, neuralgia, axonal neuropathy

[7] Includes myalgia, bone pain, back pain, spinal pain, musculoskeletal chest pain, pain in extremity, neck pain, non-cardiac chest pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal pain

[8] Includes arthralgia, arthritis

Table 6: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Early Stage NSCLC Receiving Intravenous Atezolizumab in IMpower010

Laboratory Abnormality[1]	Intravenous Atezolizumab [2]		Best Supportive Care[2]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased aspartate aminotransferase	34	2.5	18	0
Increased alanine aminotransferase	30	3.3	19	0.4
Hyperkalemia	24	3.5	15	2.5
Increased blood creatinine	31	0.2	23	0.2

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

[2] The denominators used to calculate the rate varied from 78-480 for BSC arm and 483 for intravenous atezolizumab are for all tests of interest based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

The safety of intravenous atezolizumab was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naïve patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received intravenous atezolizumab 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. IMpower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area). The median duration of exposure to intravenous atezolizumab was 5.3 months (0 to 33 months).

Fatal adverse reactions occurred in 3.8% of patients receiving intravenous atezolizumab; these included death (reported as unexplained death and death of unknown cause), aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral infarction, and device occlusion (1 patient each).

Serious adverse reactions occurred in 28% of patients receiving intravenous atezolizumab. The most frequent serious adverse reactions (>2%) were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%) and pneumonitis (2.1%)

Intravenous atezolizumab was discontinued due to adverse reactions in 6% of patients*;* the most common adverse reactions (≥2 patients) leading to intravenous atezolizumab discontinuation were peripheral neuropathy and pneumonitis.

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 26% of patients; the most common (>1%) were ALT increased (2.1%), AST increased (2.1%), pneumonitis (2.1%), pyrexia (1.4%), pneumonia (1.4%) and upper respiratory tract infection (1.4%).

Tables 7 and 8 summarize adverse reactions and selected laboratory abnormalities in patients receiving intravenous atezolizumab in IMpower110.

Table 7: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving Intravenous Atezolizumab in IMpower110

Adverse Reaction	Intravenous Atezolizumab N = 286		Platinum-Based Chemotherapy N = 263	
	All Grades (%)	Grades 3–4* (%)	All Grades* (%)	Grades 3–4 (%)
Gastrointestinal				
Nausea	14	0.3	34	1.9
Constipation	12	1.0	22	0.8
Diarrhea	11	0	12	0.8
General				
Fatigue/Asthenia	25	1.4	34	4.2
Pyrexia	14	0	9	0.4
Metabolism and Nutrition				
Decreased appetite	15	0.7	19	0
Respiratory, Thoracic and Mediastinal				
Dyspnea	14	0.7	10	0
Cough	12	0.3	10	0

Graded per NCI CTCAE v4.0

Table 8: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving Intravenous Atezolizumab in IMpower110

Laboratory Abnormality	Intravenous Atezolizumab		Platinum Based Chemotherapy	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	69	1.8	94	20
Lymphopenia	47	9	59	17
Chemistry				
Hypoalbuminemia	48	0.4	39	2
Increased alkaline phosphatase	46	2.5	42	1.2
Hyponatremia	44	9	36	7
Increased ALT	38	3.2	32	0.8
Increased AST	36	3.2	32	0.8
Hyperkalemia	29	3.9	36	2.7
Hypocalcemia	24	1.4	24	2.7
Increased blood creatinine	24	0.7	33	1.5
Hypophosphatemia	23	3.6	21	2

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: intravenous atezolizumab (range: 278-281); platinum-based chemotherapy (range:256-260). Graded per NCI CTCAE v4.0. Increased blood creatinine only includes patients with test results above the normal range.

First-Line Metastatic Non-squamous NSCLC

IMpower150

The safety of intravenous atezolizumab with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received intravenous atezolizumab 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min intravenously every 3 weeks for a maximum of 4 or 6 cycles, followed by intravenous atezolizumab 1200 mg with bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. The median duration of exposure to intravenous atezolizumab was 8.3 months in patients receiving intravenous atezolizumab with bevacizumab, paclitaxel, and carboplatin.

Fatal adverse reactions occurred in 6% of patients receiving intravenous atezolizumab; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions (>2%) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis.

Intravenous atezolizumab was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities in patients receiving intravenous atezolizumab with bevacizumab, paclitaxel, and carboplatin in IMpower150.

Table 9: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving Intravenous Atezolizumab in IMpower150

Adverse Reaction	Intravenous Atezolizumab with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy.

[2] Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform.

[3] Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, backpain, myalgia, and bone pain.

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis.

[5] Based on adverse reaction terms since laboratory data for proteinuria was not systematically collected.

Table 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving Intravenous Atezolizumab in IMpower150

Laboratory Abnormality	Intravenous Atezolizumab with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA[1]	44	NA[1]
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA[1]	20	NA[1]
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	NA[1]	19	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Intravenous atezolizumab with bevacizumab, paclitaxel, and carboplatin (range: 337-380); bevacizumab, paclitaxel, and carboplatin (range: 337-382). Graded per NCI CTCAE v4.0

[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

IMpower130

The safety of intravenous atezolizumab with paclitaxel protein-bound and carboplatin was evaluated in IMpower130, a multicenter, international, randomized, open-label trial in which 473 chemotherapy-naïve patients with metastatic non-squamous NSCLC received intravenous atezolizumab 1200 mg and carboplatin AUC 6 mg/mL/min intravenously on Day 1 and paclitaxel protein-bound 100 mg/m^2 intravenously on Days 1, 8, and 15 of each 21-day cycle for a maximum of 4 or 6 cycles, followed by intravenous atezolizumab 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. Among patients receiving intravenous atezolizumab, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Fatal adverse reactions occurred in 5.3% of patients receiving intravenous atezolizumab; these included pneumonia (1.1%), pulmonary embolism (0.8%), myocardial infarction (0.6%), cardiac arrest (0.4%), pneumonitis (0.4%) and sepsis, septic shock, staphylococcal sepsis, aspiration, respiratory distress, cardiorespiratory arrest, ventricular tachycardia, death (not otherwise specified), and hepatic cirrhosis (0.2% each).

Serious adverse reactions occurred in 51% of patients receiving intravenous atezolizumab. The most frequent serious adverse reactions (≥2%) were pneumonia (6%), diarrhea (3%), lung infection (3%), pulmonary embolism (3%), chronic obstructive pulmonary disease exacerbation (2.5%), dyspnea (2.3%), and febrile neutropenia (1.9%).

Intravenous atezolizumab was discontinued due to adverse reactions in 13% of patients; the most common adverse reactions leading to discontinuation were pneumonia (0.8%), pulmonary embolism (0.8%), fatigue (0.6%), dyspnea (0.6%), pneumonitis (0.6%), neutropenia (0.4%), nausea (0.4%), renal failure (0.4%), cardiac arrest (0.4%), and septic shock (0.4%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 62% of patients; the most common (>1%) were neutropenia, thrombocytopenia, anemia, diarrhea, fatigue/asthenia, pneumonia, dyspnea, pneumonitis, pyrexia, nausea, acute kidney injury, vomiting, pulmonary embolism, arthralgia, infusion-related reaction, abdominal pain, chronic obstructive pulmonary disease exacerbation, dehydration, and hypokalemia.

Tables 11 and 12 summarize adverse reactions and laboratory abnormalities in patients receiving intravenous atezolizumab with paclitaxel protein-bound and carboplatin in IMpower130.

Table 11: Adverse Reactions Occurring in ≥20% of Patients with NSCLC Receiving Intravenous Atezolizumab in IMpower130

Adverse Reaction	Intravenous Atezolizumab with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/Asthenia	61	11	60	8
Gastrointestinal				
Nausea	50	3.4	46	2.2

Diarrhea [1]	43	6	32	6
Constipation	36	1.1	31	0
Vomiting	27	2.7	19	2.2
Musculoskeletal and Connective Tissue				
Myalgia/Pain [2]	38	3	22	0.4
Nervous System				
Neuropathy [3]	33	2.5	28	2.2
Respiratory, Thoracic and Mediastinal				
Dyspnea [4]	32	4.9	25	1.3
Cough	27	0.6	17	0
Skin and Subcutaneous Tissue				
Alopecia	32	0	27	0
Rash [5]	20	0.6	11	0.9
Metabolism and Nutrition				
Decreased appetite	30	2.1	26	2.2

Graded per NCI CTCAE v4.0
[1] Includes diarrhea, colitis, and gastroenteritis
[2] Includes back pain, pain in extremity, myalgia, musculoskeletal chest pain, bone pain, neck pain and musculoskeletal discomfort
[3] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy
[4] Includes dyspnea, dyspnea exertional and wheezing
[5] Includes rash, rash maculo-papular, eczema, rash pruritic, rash erythematous, dermatitis, dermatitis contact, drug eruption, seborrheic dermatitis and rash macular.

Table 12: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving Intravenous Atezolizumab in IMpower130

Laboratory Abnormality	**Intravenous Atezolizumab with Paclitaxel Protein-Bound and Carboplatin N = 473**		**Paclitaxel Protein-Bound and Carboplatin N = 232**	
	All Grades (%)	**Grades 3–4 (%)**	**All Grades (%)**	**Grades 3–4 (%)**
Hematology				
Anemia	92	33	87	25
Neutropenia	75	50	67	39
Thrombocytopenia	73	19	59	13
Lymphopenia	71	23	61	16
Chemistry				
Hyperglycemia	75	8	66	8
Hypomagnesemia	50	3.4	42	3.2
Hyponatremia	37	9	28	7

Hypoalbuminemia	35	1.3	31	0
Increased ALT	31	2.8	24	3.9
Hypocalcemia	31	2.6	27	1.8
Hypophosphatemia	29	6	20	3.2
Increased AST	28	2.2	24	1.8
Increased TSH	26	NA[1]	5	NA[1]
Hypokalemia	26	6	24	4.4
Increased Alkaline Phosphatase	25	2.6	22	1.3
Increased Blood Creatinine	23	2.8	16	0.4
Hyperphosphatemia	21	NA[1]	13	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous atezolizumab with paclitaxel protein bound and carboplatin (range: 423 - 467); paclitaxel protein bound and carboplatin (range: 218- 229). Graded per NCI CTCAE v4.0.
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

Previously Treated Metastatic NSCLC

OAK

The safety of intravenous atezolizumab was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. A total of 609 patients received intravenous atezolizumab 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The median duration of exposure was 3.4 months (0 to 26 months) in intravenous atezolizumab-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had Eastern Cooperative Oncology Group (ECOG) performance status of 1.

Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

Intravenous atezolizumab was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to intravenous atezolizumab discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of intravenous atezolizumab occurred in 25% of patients; the most common (>1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain.

Tables 13 and 14 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 13: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving Intravenous Atezolizumab in OAK

Adverse Reaction	Intravenous Atezolizumab N = 609		Docetaxel N = 578	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue/Asthenia[1]	44	4	53	6
Pyrexia	18	<1	13	<1
1. RESPIRATORY				
Cough[2]	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
Metabolism and Nutrition				
Decreased appetite	23	<1	24	1.6
2. MUSCULOSKELETAL				
Myalgia/Pain[3]	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
3. GASTROINTESTINAL				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
4. SKIN				
Rash[4]	12	<1	10	0

Graded per NCI CTCAE v4.0
[1] Includes fatigue and asthenia
[2] Includes cough and exertional cough
[3] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia
[4] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 14: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving Intravenous Atezolizumab in OAK

Laboratory Abnormality	Intravenous Atezolizumab		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4

Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous atezolizumab (range: 546□585) and docetaxel (range: 532□560). Graded according to NCI CTCAE version 4.0

Adverse Reactions in Adult Patients with Small Cell Lung Cancer

The safety of TECENTRIQ 1875MG/15ML SC for its approved Small Cell Lung Cancer (SCLC) indication *[see Indications and Usage (1.2)]* has been established in adequate and well-controlled studies of intravenous atezolizumab for SCLC (IMpower133 study).

Small Cell Lung Cancer (SCLC)

IMpower133

The safety of intravenous atezolizumab with carboplatin and etoposide was evaluated in IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial in which 198 patients with ES-SCLC received intravenous atezolizumab 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by intravenous atezolizumab 1200 mg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.4)]*. Among 198 patients receiving intravenous atezolizumab, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

Fatal adverse reactions occurred in 2% of patients receiving intravenous atezolizumab. These included pneumonia, respiratory failure, neutropenia, and death (1 patient each).

Serious adverse reactions occurred in 37% of patients receiving intravenous atezolizumab. Serious adverse reactions in >2% were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%).

Intravenous atezolizumab was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Tables 15 and 16 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received intravenous atezolizumab with carboplatin and etoposide in IMpower133.

Table 15: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving Intravenous Atezolizumab in IMpower133

Adverse Reaction	Intravenous Atezolizumab with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)

General				
Fatigue/Asthenia	39	5	33	3
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

Graded per NCI CTCAE v4.0

Table 16: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving Intravenous Atezolizumab in IMpower133

Laboratory Abnormality	Intravenous Atezolizumab with Carboplatin and Etoposide		Placebo with Carboplatin and Etoposide	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[2]	28	NA[1]	15	NA[1]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia	21	NA[1]	23	NA[1]
Increased TSH[2]	21	NA[1]	7	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous atezolizumab (range: 181-193); Placebo (range: 181-196). Graded per NCI CTCAE v4.0

[1] NA= Not applicable. [2] TSH = thyroid-stimulating hormone. NCI CTCAE v4.0 does not include these laboratories.

Adverse Reactions in Adult Patients with Urothelial Carcinoma

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of intravenous atezolizumab was evaluated in IMvigor 210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy *[see Clinical Studies (14.1)]*. Patients received intravenous atezolizumab 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

Five patients (4.2%) who were treated with intravenous atezolizumab experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death.

Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

Intravenous atezolizumab was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%).

Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion- related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism.

Tables 17 and 18 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received intravenous atezolizumab in IMvigor210 (Cohort 1).

Table 17: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	Intravenous Atezolizumab N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2

Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[6]	17	0.8
Infections		
Urinary tract infection[7]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[8]	14	0
Dyspnea[9]	12	0

[1] Includes fatigue, asthenia, lethargy, and malaise
[2] Includes edema peripheral, scrotal edema, lymphedema, and edema
[3] Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
[4] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
[5] Includes decreased appetite and early satiety
[6] Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
[7] Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
[8] Includes cough and productive cough
[9] Includes dyspnea and exertional dyspnea

Table 18: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Laboratory Abnormality	**Grades 3–4 (%)**
Chemistry	
Hyponatremia	15
Hyperglycemia	10
Increased Alkaline Phosphatase	7
Increased Creatinine	5

Hypophosphatemia	4
Increased ALT	4
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3
Hematology	
Lymphopenia	9
Anemia	7

Graded per NCI CTCAE v4.0.

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of intravenous atezolizumab was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received intravenous atezolizumab 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

Three patients (1%) who were treated with intravenous atezolizumab experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

Intravenous atezolizumab was discontinued for adverse reactions in 3.2% of patients. Sepsis led to discontinuation in 0.6% of patients.

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Adverse reactions leading to interruption occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis.

Tables 19 and 20 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received intravenous atezolizumab in IMvigor210 (Cohort 2).

Table 19: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

Adverse Reaction	**Intravenous Atezolizumab N = 310**	
	All Grades (%)	**Grades 3–4 (%)**
General		
Fatigue	52	6

Pyrexia	21	1
Peripheral edema	18	1
Metabolism and Nutrition		
Decreased appetite	26	1
Gastrointestinal		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
Infections		
Urinary tract infection	22	9
Respiratory, Thoracic, and Mediastinal		
Dyspnea	16	4
Cough	14	0.3
Musculoskeletal and Connective Tissue		
Back/Neck pain	15	2
Arthralgia	14	1
Skin and Subcutaneous Tissue		
Rash	15	0.3
Pruritus	13	0.3
Renal and Urinary		
Hematuria	14	3

Table 20: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

Laboratory Abnormality	**Grades 3–4 (%)**
Chemistry	
Hyponatremia	10
Hyperglycemia	5
Increased Alkaline Phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2

Hypoalbuminemia	1
Hematology	
Lymphopenia	10
Anemia	8

Graded per NCI CTCAE v4.0.

Adverse Reactions in Adult Patients with TNBC

Metastatic Triple Negative Breast Cancer (TNBC)

The safety of intravenous atezolizumab in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blinded placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease *[see Clinical Studies (14.3)]*. Patients received intravenous atezolizumab 840 mg (n=452) or placebo (n=438) intravenously followed by paclitaxel protein-bound (100 mg/m^2) intravenously. For each 28 day cycle, intravenous atezolizumab was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to intravenous atezolizumab was 5.5 months (range: 0-32 months) and paclitaxel protein-bound was 5.1 months (range: 0-31.5 months) in the intravenous atezolizumab and paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0-23.7 months) in the placebo and paclitaxel protein-bound arm.

Fatal adverse reactions occurred in 1.3%) of patients in the intravenous atezolizumab and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism.

Serious adverse reactions occurred in 23% of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspnea (1%), and pyrexia (1%).

Adverse reactions leading to discontinuation of intravenous atezolizumab occurred in 6% (29/452) of patients in the intravenous atezolizumab and paclitaxel protein-bound arm. The most common adverse reaction leading to intravenous atezolizumab discontinuation was peripheral neuropathy (<1%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 31% of patients; the most common (≥ 2%) were neutropenia, neutrophil count decreased, hyperthyroidism, and pyrexia.

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the intravenous atezolizumab and paclitaxel protein-bound arm.

Tables 21 and 22 summarize adverse reactions and selected laboratory abnormalities worsening from baseline in the intravenous atezolizumab treated patients.

Table 21: Adverse Reactions Occurring in ≥10% of Patients with TNBC in IMpassion130

Adverse Reaction	**Intravenous Atezolizumab with Paclitaxel Protein-Bound N = 452**		**Placebo with Paclitaxel Protein-Bound N = 438**	
	All Grades (%)	**Grades 3–4 (%)**	**All Grades (%)**	**Grades 3–4 (%)**

Skin and Subcutaneous Tissue				
Alopecia	56	<1	58	<1
Rash	17	<1	16	<1
Pruritus	14	0	10	0
Nervous System				
Peripheral neuropathies[1]	47	9	44	5
Headache	23	<1	22	<1
Dysgeusia	14	0	14	0
Dizziness	14	0	11	0
General				
Fatigue	47	4	45	3.4
Pyrexia	19	<1	11	0
Peripheral Edema	15	<1	16	1.4
Asthenia	12	<1	11	<1
Gastrointestinal				
Nausea	46	1.1	38	1.8
Diarrhea	33	1.3	34	2.1
Constipation	25	<1	25	<1
Vomiting	20	<1	17	1.1
Abdominal pain	10	<1	12	<1
Respiratory, Thoracic, and Mediastinal				
Cough	25	0	19	0
Dyspnea	16	<1	15	<1
Metabolism and Nutrition				
Decreased Appetite	20	<1	18	<1
Musculoskeletal and Connective Tissue				
Arthralgia	18	<1	16	<1
Back pain	15	1.3	13	<1
Myalgia	14	<1	15	<1
Pain in extremity	11	<1	10	<1
Endocrine				
Hypothyroidism	14	0	3.4	0
Infections				
Urinary tract infection	12	<1	11	<1
Upper respiratory tract infection	11	1.1	9	0
Nasopharyngitis	11	0	8	0

Graded per NCI CTCAE v4.0

1 Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 22: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with TNBC in IMpassion130

Laboratory Abnormality	Intravenous Atezolizumab with Paclitaxel Protein-Bound		Placebo in combination with Paclitaxel Protein-Bound	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Hemoglobin	79	3.8	73	3
Decreased Leukocytes	76	14	71	9
Decreased Neutrophils	58	13	54	13
Decreased Lymphocytes	54	13	47	8
Increased Prothrombin INR	25	<1	25	<1
Chemistry				
Increased ALT	43	6	34	2.7
Increased AST	42	4.9	34	3.4
Decreased Calcium	28	1.1	26	<1
Decreased Sodium	27	4.2	25	2.7
Decreased Albumin	27	<1	25	<1
Increased Alkaline Phosphatase	25	3.3	22	2.7
Decreased Phosphate	22	3.6	19	3.7
Increased Creatinine	21	<1	16	<1

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: intravenous atezolizumab with paclitaxel protein-bound (range: 316-452); placebo with paclitaxel protein-bound (range: 299-438). Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

Adverse Reactions in Adult Patients with Hepatocellular Carcinoma

The safety of TECENTRIQ 1875MG/15ML SC for its approved indication hepatocellular carcinoma *[see Indications and Usage (1.5)]* has been established in adequate and well-controlled studies of intravenous atezolizumab for hepatocellular carcinoma (IMbrave150 study).

Hepatocellular Carcinoma

IMbrave150

The safety of intravenous atezolizumab in combination with bevacizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.5)]*. Patients received 1,200 mg of intravenous atezolizumab intravenously followed by 15 mg/kg bevacizumab (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to intravenous atezolizumab was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the intravenous atezolizumab and bevacizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the intravenous atezolizumab and bevacizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of intravenous atezolizumab occurred in 9% of patients in the intravenous atezolizumab and bevacizumab arm. The most common adverse reactions leading to intravenous atezolizumab discontinuation were hemorrhages (1.2%), including gastrointestinal, subarachnoid, and pulmonary hemorrhages; increased transaminases or bilirubin (1.2%); infusion-related reaction/cytokine release syndrome (0.9%); and autoimmune hepatitis (0.6%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 41% of patients in the intravenous atezolizumab and bevacizumab arm; the most common (≥ 2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (8%); infections (6%); gastrointestinal hemorrhages (3.6%); thrombocytopenia/decreased platelet count (3.6%); hyperthyroidism (2.7%); and pyrexia (2.1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12% of patients in the intravenous atezolizumab and bevacizumab arm.

Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received intravenous atezolizumab and bevacizumab in IMbrave150.

Table 23: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Intravenous Atezolizumab in IMbrave150

Adverse Reaction	Intravenous Atezolizumab in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[2] (%)	Grades 3–4[2] (%)	All Grades[2] (%)	Grades 3–4[2] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/Asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6

Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

Table 24: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving Intravenous Atezolizumab in IMbrave150

Laboratory Abnormality	**Intravenous Atezolizumab in combination with Bevacizumab (n=329)**		**Sorafenib (n=156)**	
	All Grades[1] (%)	**Grades 3–4[1] (%)**	**All Grades[1] (%)**	**Grades 3–4[1] (%)**
Chemistry				
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3

Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous atezolizumab plus bevacizumab (222-323) and sorafenib (90-153)
[1] Graded per NCI CTCAE v4.0

Adverse Reactions in Adult Patients with Melanoma

The safety of TECENTRIQ 1875MG/15ML SC for its approved melanoma indication *[see Indications and Usage (1.4)]* has been established in adequate and well-controlled studies of intravenous atezolizumab for melanoma (IMspire150 study).

Metastatic Melanoma

IMspire150

The safety of intravenous atezolizumab, administered with cobimetinib and vemurafenib was evaluated in IMspire150, a double-blind, randomized (1:1), placebo-controlled study conducted in patients with previously untreated BRAF V600 mutation-positive metastatic or unresectable melanoma *[see Clinical Studies (14.6)]*. Patients received intravenous atezolizumab with cobimetinib and vemurafenib (n=230) or placebo with cobimetinib and vemurafenib (n=281).

Among the 230 patients who received intravenous atezolizumab administered with cobimetinib and vemurafenib, the median duration of exposure to intravenous atezolizumab was 9.2 months (range: 0-30 months) to cobimetinib was 10.0 months (range: 1-31 months) and to vemurafenib was 9.8 months (range: 1-31 months).

Fatal adverse reactions occurred in 3% of patients in the intravenous atezolizumab plus cobimetinib and vemurafenib arm. Adverse reactions leading to death were hepatic failure, fulminant hepatitis, sepsis, septic shock, pneumonia, and cardiac arrest.

Serious adverse reactions occurred in 45% of patients in the intravenous atezolizumab plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) serious adverse reactions were hepatotoxicity (7%), pyrexia (6%), pneumonia (4.3%), malignant neoplasms (2.2%), and acute kidney injury (2.2%).

Adverse reactions leading to discontinuation of intravenous atezolizumab occurred in 21% of patients in the intravenous atezolizumab plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to intravenous atezolizumab discontinuation were increased ALT (2.2%) and pneumonitis (2.6%).

Adverse reactions leading to interruption of intravenous atezolizumab occurred in 68% of patients in the intravenous atezolizumab plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to intravenous atezolizumab interruption were pyrexia (14%), increased ALT (13%), hyperthyroidism (10%), increased AST (10%), increased lipase (9%), increased amylase (7%), pneumonitis (5%), increased CPK (4.3%), diarrhea (3.5%), pneumonia (3.5%), asthenia (3%), rash (3%), influenza (3%), arthralgia (2.6%), fatigue (2.2%), dyspnea (2.2%), cough (2.2%), peripheral edema (2.2%), uveitis (2.2%), bronchitis (2.2%), hypothyroidism (2.2%), and respiratory tract infection (2.2%).

Tables 25 and 26 summarize the incidence of adverse reactions and laboratory abnormalities in IMspire150.

Table 25: Adverse Reactions Occurring in ≥10% of Patients on the Intravenous Atezolizumab plus Cobimetinib and Vemurafenib Arm or the Placebo

plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4 Intravenous Atezolizumab in IMspire150)

Adverse Reaction	Intravenous Atezolizumab in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash [1]	75	27	72	23
Pruritus	26	< 1	17	<1
Photosensitivity reaction	21	<1	25	3.2
General Disorders and Administration Site Conditions				
Fatigue [2]	51	3	45	1.8
Pyrexia [3]	49	1.7	35	2.1
Edema [4]	26	<1	21	0
Gastrointestinal Disorders				
Hepatotoxicity [5]	50	21	36	13
Nausea	30	<1	32	2.5
Stomatitis [6]	23	1.3	15	<1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain [7]	62	4.3	48	3.2
Endocrine Disorders				
Hypothyroidism [8]	22	0	10	0
Hyperthyroidism	18	<1	8	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction [9]	10	2.6	8	<1
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis [10]	12	1.3	6	<1
Vascular Disorders				
Hypertension [11]	17	10	18	7

[1] Includes rash, rash maculo-papular, dermatitis acneiform, rash macular, rash erythematous, eczema, skin exfoliation, rash papular, rash pustular, palmar-plantar erythrodysaesthesia syndrome, dermatitis, dermatitis contact, erythema multiforme, rash pruritic, drug eruption, nodular rash, dermatitis allergic, exfoliative rash, dermatitis exfoliative generalised and rash morbilliform

[2] Includes fatigue, asthenia and malaise

[3] Includes pyrexia and hyperpyrexia

[4] Includes edema peripheral, lymphoedema, oedema, face oedema, eyelid oedema, periorbital oedema, lip oedema and generalised oedema

[5] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased, hepatitis, hepatic enzyme increased, hepatotoxicity, hypertransaminasaemia, bilirubin conjugated increased, hepatocellular injury, hyperbilirubinaemia, liver function test increased, hepatic failure, hepatitis fulminant and liver function test abnormal

[6] Includes stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, cheilitis and glossitis

[7] Includes arthralgia, myalgia, pain in extremity, back pain, musculoskeletal pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, bone pain, spinal pain, immune-mediated arthritis, joint stiffness and non-cardiac chest pain

[8] Includes hypothyroidism and blood thyroid stimulating hormone increased

[9] Includes infusion related reaction and hypersensitivity

[10] Includes pneumonitis and interstitial lung disease

[11] Includes hypertension, blood pressure increased, hypertensive crisis

Clinically important adverse reactions in < 10% of patients who received intravenous atezolizumab plus cobimetinib and vemurafenib were:

Cardiac Disorders: Arrhythmias, ejection fraction decreased, electrocardiogram QT prolonged

Eye Disorders: Uveitis

Gastrointestinal disorders: Pancreatitis

Infections and infestations: Pneumonia, urinary tract infection

Metabolism and nutrition disorders: Hyperglycemia

Nervous system Disorders: Dizziness, dysgeusia, syncope

Respiratory, thoracic and mediastinal disorders: Dyspnea, oropharyngeal pain

Skin and Subcutaneous Tissue Disorders: Vitiligo

Table 26: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving Intravenous Atezolizumab Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) in IMspire150

Laboratory Abnormality	**Intravenous Atezolizumab in combination with Cobimetinib and Vemurafenib (n=230)**		**Placebo with Cobimetinib and Vemurafenib (n=281)**	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Lymphocytes	80	24	72	17
Decreased Hemoglobin	77	2.6	72	2.2
Decreased Platelet	34	1.3	24	0.4
Decreased Neutrophils	26	2.2	19	1.5
Chemistry				
Increased Creatine Kinase	88	22	81	18
Increased AST	80	13	68	6
Increased ALT	79	18	62	12
Increased Triacylglycerol Lipase	75	46	62	35
Increased Alkaline Phosphatase	73	6	63	2.9
Decreased Phosphorus	67	22	64	14
Increased Amylase	51	13	45	13
Increased Blood Urea Nitrogen	47	NA[1]	37	NA[1]
Decreased Albumin	43	0.9	34	1.5
Increased Bilirubin	42	3.1	33	0.7
Decreased Calcium	41	1.3	28	0
Decreased Sodium	40	5	34	7
Decreased Thyroid-Stimulating Hormone	38	NA[1]	23	NA[1]
Increased Thyroid-Stimulating Hormone [2]	37	NA[1]	33	NA[1]
Decreased Potassium	36	5	22	4.3
Increased Triiodothyronine	33	NA[1]	18	NA[1]
Increased Free Thyroxine	32	NA[1]	21	NA[1]

Decreased Total Triiodothyronine	32	NA[1]	8	NA[1]
Increased Potassium	29	1.3	19	1.4
Decreased Triiodothyronine	27	NA[1]	21	NA[1]
Increased Sodium	20	0	13	0.4

Graded per NCI CTCAE v4.0.
Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: intravenous atezolizumab plus cobimetinib and vemurafenib (28-277), placebo plus cobimetinib and vemurafenib arm (25-230).
[1] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.
[2] Increased Thyroid Stimulating Hormone has a difference <5% (All Grades) between arms and is included for clinical completeness.

Adverse Reactions in Adults with Alveolar Soft Part Sarcoma

The safety of TECENTRIQ 1875MG/15ML SC for its approved alveolar soft part sarcoma (ASPS) indication *[see Indications and Usage (1.5)]* has been established in adequate and well-controlled studies of intravenous atezolizumab for ASPS (ML39345 study).

Alveolar Soft Part Sarcoma

ML39345 Study

The safety of intravenous atezolizumab was evaluated in 47 adult and 2 pediatric patients enrolled in Study ML39345 *[see Clinical Studies (14.7)]*. Adult patients received intravenous atezolizumab 1200 mg every 3 weeks and pediatric patients received 15 mg/kg up to a maximum 1200 mg every 3 weeks until disease progression or unacceptable toxicity. The median duration of exposure to intravenous atezolizumab was 8.9 months (1 to 40 months).

Serious adverse reactions occurred in 41% of patients receiving intravenous atezolizumab. The most frequent serious adverse reactions (>2%) were fatigue, pain in extremity, pulmonary hemorrhage, and pneumonia (4.1% each).

Dosage interruptions of intravenous atezolizumab due to an adverse reaction occurred in 35% of patients. The most common adverse reactions (≥3%) leading to dose interruptions were pneumonitis and pain in extremity (4.1% each).

Tables 27 and 28 summarize adverse reactions and laboratory abnormalities in Study ML39345.

Table 27: Adverse Reactions Occurring in ≥15% of Patients with ASPS Receiving Intravenous Atezolizumab in ML39345

Adverse Reaction	Intravenous Atezolizumab N = 49	
	All Grades (%)	Grades 3–4 (%)
General disorders and administration site conditions		
Fatigue	55	2
Pyrexia	25	2
Influenza like illness	18	0
Gastrointestinal disorders		
Nausea	43	0
Vomiting	37	0

Constipation	33	0
Diarrhea	27	2
Abdominal pain[1]	25	0
Metabolism and nutrition disorders		
Decreased appetite	22	2
Respiratory, Thoracic and Mediastinal		
Cough[2]	45	0
Dyspnea	33	0
Rhinitis allergic	16	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[3]	67	8
Skin and subcutaneous tissue disorders		
Rash[4]	47	2
Nervous system disorders		
Headache	43	4
Dizziness[5]	29	4
Vascular disorders		
Hypertension	43	6
Hemorrhage[6]	29	2
Psychiatric disorders		
Insomnia	27	0
Anxiety	25	0
Cardiac Disorders		
Arrhythmia[7]	22	2
Endocrine disorders		
Hypothyroidism[8]	25	0
Investigations		
Weight decreased	18	0
Weight increased	16	6

Graded per NCI CTCAE v4.0

[1]Includes abdominal pain and abdominal pain upper
[2]Includes cough, upper-airway cough syndrome, and productive cough
[3]Includes arthralgia, pain in extremity, myalgia, non-cardiac chest pain, neck pain, musculoskeletal chest pain, and back pain
[4]Includes rash maculo-papular, rash, dermatitis acneiform, eczema, skin exfoliation, and drug eruption
[5]Includes vertigo and dizziness
[6]Includes pulmonary hemorrhage, hemoptysis, conjunctival hemorrhage, epistaxis, hematuria, rectal hemorrhage, and laryngeal hemorrhage
[7]Includes atrial fibrillation, sinus bradycardia, ventricular tachycardia, and sinus tachycardia
[8]Includes hypothyroidism and blood thyroid stimulating hormone increased

Table 28: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with ASPS Receiving Intravenous Atezolizumab in ML39345

Laboratory Abnormality [1]	Intravenous Atezolizumab [2]	
	All Grades (%)	Grades 3–4 (%)
Hematology		
Decreased Hemoglobin	63	0
Decreased Platelets	27	0
Increased Platelets	29	0
Chemistry		
Increased Alkaline Phosphatase	29	0
Decreased Amylase	40	0
Increased Amylase	20	20
Decreased Bilirubin	49	0
Decreased Calcium	47	0
Increased Calcium	25	14
Decreased Glucose	33	0
Increased Glucose	78	0
Decreased Glucose (fasting)	25	0
Decreased Magnesium	21	0
Increased Magnesium	26	26
Increased AST	39	2
Increased ALT	33	2
Decreased Sodium	43	0
Increased Lipase	25	25

[1] Laboratory tests which do not have NCI CTCAE grading criteria are also included for All Grade assessments, which were performed by comparing to respective lab normal ranges.
[2] The denominators used to calculate the rate varied from 4-49 for all tests of interest based on the number of patients with a baseline value and at least one on-study laboratory measurement available.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of intravenous atezolizumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac: pericarditis, pericardial effusion, cardiac tamponade
- Musculoskeletal and Connective Tissue: tenosynovitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any

suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, TECENTRIQ 1875MG/15ML SC can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ 1875MG/15ML SC in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *(see Data)*. Advise females of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.4)]*.

Data

Animal Data

TECENTRIQ 1875MG/15ML SC for subcutaneous injection contains atezolizumab and hyaluronidase *[see Description (11)]*.

Atezolizumab: Animal reproduction studies have not been conducted with atezolizumab to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering atezolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Hyaluronidase: In an embryo-fetal study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is > 2,400 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 400 times higher than the human dose.

In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase (recombinant human) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is > 1,200 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab or hyaluronidase in human milk or its effects on the breastfed child, or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TECENTRIQ 1875MG/15ML SC are unknown. Because of the potential for serious adverse reactions in breastfed children from TECENTRIQ 1875MG/15ML SC, advise women not to breastfeed during treatment with TECENTRIQ 1875MG/15ML SC and for 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, TECENTRIQ 1875MG/15ML SC can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ 1875MG/15ML SC *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ 1875MG/15ML SC and for 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ 1875MG/15ML SC may impair fertility in females of reproductive potential while receiving TECENTRIQ 1875MG/15ML SC treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ 1875MG/15ML SC have not been established in pediatric patients.

8.5 Geriatric Use

Of 247 adult patients treated with TECENTRIQ 1875MG/15ML SC as monotherapy in IMscin001, 45% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness of TECENTRIQ 1875MG/15ML SC have been observed between patients aged 65 years or older and younger adult patients.

The safety of TECENTRIQ 1875MG/15ML SC as monotherapy or in combination with other antineoplastic drugs for its approved indications *[see Indications and Usage (1.1, 1.2, 1.3, 1.4, 1.5)]* has been established in adequate and well-controlled studies of intravenous atezolizumab as a single agent and in combination with other antineoplastic drugs. Below is a description of geriatric use information from the intravenous atezolizumab studies.

Of 3040 patients with urothelial carcinoma, lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma who were treated with intravenous atezolizumab in clinical studies, 43% were 65 years and over and 12% were 75 years and over.

No overall differences in safety or effectiveness were observed between intravenous atezolizumab-treated patients aged 65 years or older and younger adult patients.

11 DESCRIPTION

TECENTRIQ 1875MG/15ML SC is a fixed-combination drug product containing atezolizumab and hyaluronidase (human recombinant).

- Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Atezolizumab is an Fc-engineered, humanized, non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.
- Hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs administered subcutaneously. It is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

TECENTRIQ 1875MG/15ML SC (atezolizumab and hyaluronidase) injection for subcutaneous use is a sterile, preservative-free, clear, colorless to slightly yellowish liquid in single-dose vials. Each 15 mL single-dose vial contains 1875mg of atezolizumab, 30,000 units of hyaluronidase , sucrose, L-histidine, L-methionine , polysorbate 20, and water for injection adjusted to pH 5.8 with acetic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

In mouse models of cancer, dual inhibition of the PD-1/PD-L1 and MAPK pathways suppresses tumor growth and improves tumor immunogenicity through increased antigen presentation and T cell infiltration and activation compared to targeted therapy alone.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days.

Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in TECENTRIQ 1875MG/15ML SC acts transiently and locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of atezolizumab and hyaluronidase have not been fully characterized.

12.3 Pharmacokinetics

When comparing atezolizumab exposure following subcutaneous TECENTRIQ 1875MG/15ML SC to that of intravenous atezolizumab in Study IMscin001 *[see Clinical Studies (14.2)]*, the geometric mean ratio (GMR) (90% CI) for Cycle 1 C_{trough} was 1.05 (0.88, 1.24) and $AUC_{0\text{-}21days}$ was 0.87 (0.83, 0.92); the steady state C_{trough} was 1.15 (1.05, 1.26) and AUC was 1.01 (0.94, 1.08).

Steady-state was achieved 6 to 9 weeks. The systemic accumulation ratio following administration of the approved recommended dosage of TECENTRIQ 1875MG/15ML SC was 2.2.

Absorption

The mean absolute bioavailability (CV%) of atezolizumab was 72% (83%) and the median time (range) to reach maximum atezolizumab concentration (T_{max}) was 4.5 (2.2, 9) days.

Distribution

The volume of distribution of atezolizumab at steady state was 6.9 L.

Elimination

The atezolizumab clearance (CV%) was 0.2 L/day (29%) and the terminal half-life was 27 days. Atezolizumab clearance decreased over time, with a mean maximal reduction (CV%) from baseline value of 17% (41%); this decrease in clearance is not considered clinically significant.

Specific Populations

No clinically significant differences in the pharmacokinetics of atezolizumab were observed based on age, body weight, sex, albumin levels, tumor burden, region ,race, mild or moderate renal impairment (estimated glomerular filtration rate 30 to 89 mL/minute/1.73 m^2), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST), level of PD-L1 expression, and performance status.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of TECENTRIQ 1875MG/15ML SC or of other atezolizumab products or hyaluronidase products.

During the first year of treatment in the Study IMscin001 *[see Clinical Studies (14.2)]*, the incidence of ADA was 20% (43/221) and the incidence of neutralizing antibodies (NAb) in ADA-positive patients was 54% (21/39) for TECENTRIQ 1875MG/15ML SC. The corresponding incidence of ADA was 14% (15/108) and NAb was 60% (9/15) for intravenous atezolizumab.

In Study IMscin001, atezolizumab clearance increased by 29% in patients who received TECENTRIQ 1875MG/15ML SC and who tested positive for ADA compared to patients who

tested negative for ADA; this change in clearance is not expected to be clinically significant. Because of limited immunogenicity data the effect of ADA on the effectiveness of TECENTRIQ 1875MG/15ML SC is unknown. There was no identified clinically significant effect of anti-atezolizumab antibodies on the safety of TECENTRIQ 1875MG/15ML SC during the first 6 months of treatment.

In Study IMscin001, the incidence of anti-rHuPH20 antibodies was 5.4% (12/224) and the incidence of NAb was 0% (0/12). Because of the low occurrence of anti-rHuPH20 antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics and/or safety of hyaluronidase in TECENTRIQ 1875MG/15ML SC is unknown.

Immunogenicity with Other Clinical Trials with Intravenous Atezolizumab:

During the first year of treatment with intravenous atezolizumab across clinical studies of patients with NSCLC, SCLC, HCC, and melanoma 13% to 36% of patients developed anti-atezolizumab antibodies. Across clinical studies, the NAb incidence in ADA-positive patients was 24% to 83%.

In OAK and IMbrave150, exploratory analyses showed that the subset of patients who were ADA-positive appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for ADA *[see Clinical Studies (14.2, 14.5)]*. In study IMpower150, the impact of ADA on efficacy did not appear to be clinically significant *[see Clinical Studies (14.2)]*. In the remaining studies, there is insufficient information to characterize the effect of ADA on efficacy.

Median atezolizumab clearance in patients who tested positive for ADA was 19% (range of 18% to 49%) higher as compared to atezolizumab clearance in patients who tested negative for ADA; this change in clearance is not expected to be clinically significant. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

The effect of NAb on atezolizumab exposure and safety did not appear to be clinically significant. The effect of NAb on key efficacy endpoints is uncertain due to small sample sizes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended intravenous atezolizumab dose and was reversible. There was no effect on the male monkey reproductive organs.

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. In addition, when up to 220,000 units/kg of subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks, which is > 223 times higher than the human recommended dose for hyaluronidase, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters (e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data).

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium* tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of intravenous atezolizumab was investigated in IMvigor210 (Cohort 1) (NCT02951767), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients were considered cisplatin-ineligible if they met any one of the following criteria at study entry: impaired renal function [creatinine clearance (CLcr) of 30 to 59 mL/min], Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or Grades 2-4 peripheral neuropathy. This study excluded patients who had: a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrollment; or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received intravenous atezolizumab 1200 mg as an intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), duration of response (DoR) and overall survival (OS).

In this study, the median age was 73 years, 81% were male, and 91% were White. Thirty-five percent of patients had non-bladder urothelial carcinoma and 66% had visceral metastases. Eighty percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 70% had impaired renal function, 20% had an ECOG PS of 2, 14% had a hearing loss of ≥ 25dB, and 6% had Grades 2-4 peripheral neuropathy at baseline. Twenty percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor-infiltrating IC covering < 5% of the tumor area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 16% had a hearing loss ≥ 25 dB, and

9% had Grades 2-4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 29. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%).

Table 29: Efficacy Results in IMvigor210 (Cohort 1)

	All Patients	**PD-L1 Expression Subgroups**	
	N = 119	**PD-L1 Expression of < 5% in ICs[1] N = 87**	**PD-L1 Expression of ≥ 5% in ICs[1] N = 32**
Number of IRF-assessed Confirmed Responders	28	19	9
ORR % (95% CI)	23.5% (16.2, 32.2)	21.8% (13.7, 32)	28.1% (13.8, 46.8)
Complete Response	6.7%	6.9%	6.3%
Partial Response	16.8%	14.9%	21.9%
Median DoR, months	NR	NR	NR
(range)	(3.7, 16.6+)	(3.7, 16.6+)	(8.1, 15.6+)

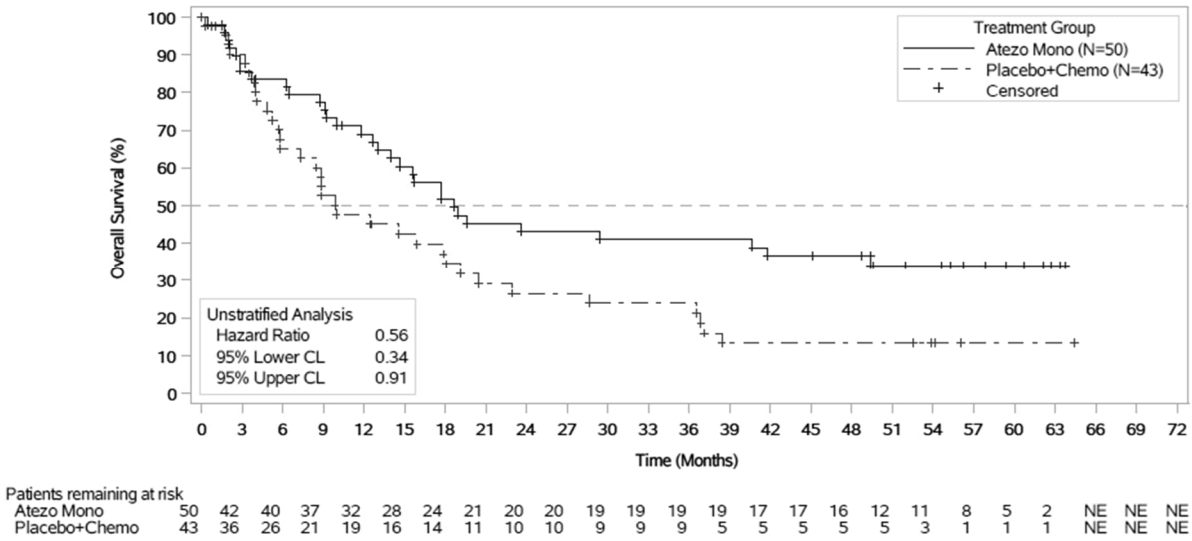
NR = Not reached
+ Denotes a censored value
[1] PD-L1 expression in tumor-infiltrating immune cells (ICs)

IMvigor130 (NCT02807636) is a phase III, multi-centre, randomised, placebo-controlled, partially blinded (Arms A and C only) study, IMvigor130, was conducted to evaluate the efficacy and safety of atezolizumab + platinum-based combination chemotherapy (i.e., either cisplatin or carboplatin with gemcitabine), Arm A, or atezolizumab monotherapy (Arm B, open-label arm) versus placebo + platinum-based combination chemotherapy (Arm C) in patients with locally advanced or metastatic UC who had not received prior systemic therapy in the metastatic setting. The co-primary efficacy outcomes were investigator-assessed progression-free survival (PFS) in Arm A versus Arm C and overall survival (OS) in Arm A versus C and then Arm B versus C, analyzed in a hierarchical fashion. Overall survival was not statistically significant for the comparison of Arm A versus Arm C, and thus no further formal testing could be conducted per the pre-defined hierarchical testing order.

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours had a low PD-L1 expression(less than5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay) was stopped after observing decreased overall survival for this subgroup at an unplanned early analysis, however, this occurred after the vast majority of patients had already been enrolled. Out of 719 patients enrolled in the atezolizumab monotherapy (n=360) and chemotherapy alone (n=359) arms, 50 and 43 patients, respectively, were cisplatin-ineligible by Galsky criteria and had tumours with high PD-L1 expression (≥ 5% of immune cells staining positive for PD-L1 by immunohistochemistry using VENTANA PD-L1 [SP142] assay). In an exploratory analysis in this subgroup of patients, the unstratified HR for OS was 0.56 (95% CI: 0.34, 0.91). The median

OS was 18.6 months (95% CI: 14.0, 49.4) in the atezolizumab monotherapy arm vs. 10.0 months (95% CI: 7.4, 18.1) in the chemotherapy alone arm (see Figure 1).

Figure 1 Kaplan-Meier Plot of Overall Survival in Cisplatin-ineligible patients whose tumours are PD-L1 high (Arm B vs. Arm C)



Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of intravenous atezolizumab was investigated in IMvigor210 (Cohort 2) (NCT02108652), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received intravenous atezolizumab 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRF using RECIST v1.1 and DoR.

In this study, the median age was 66 years, 78% were male, 91% of patients were White. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG PS of 1 and 35% of patients had a baseline CLcr < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received 2 or more prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of

the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%.

Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 30. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Table 30: Efficacy Results in IMvigor210 (Cohort 2)

	All Patients	**PD-L1 Expression Subgroups**	
	N = 310	**PD-L1 Expression of < 5% in IC[1] N = 210**	**PD-L1 Expression of ≥ 5% in IC[1] N = 100**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	14.8% (11.2, 19.3)	9.5% (5.9, 14.3)	26% (17.7, 35.7)
Complete Response	5.5%	2.4%	12.0%
Partial Response	9.4%	7.1%	14.0%
Median DOR, months (range)	27.7 (2.1+, 33.4+)	20.9 (2.1+, 33.4+)	29.7 (4.2, 31.2+)

+ Denotes a censored value
[1] PD-L1 expression in tumor-infiltrating immune cells (IC)

14.2 Non-Small Cell Lung Cancer

NSCLC - TECENTRIQ 1875MG/15ML SC

IMscin001 (NCT03735121) was an open-label, multi-center, international, randomized study conducted in adult patients with locally advanced or metastatic NSCLC who were not exposed to cancer immunotherapy and who have disease progression following platinum-based chemotherapy. Patients were excluded if they had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; received a live, attenuated vaccine within 4 weeks prior to randomization; or received systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive drugs within 2 weeks prior to randomization. A total of 371 patients were randomized 2:1 to receive either TECENTRIQ 1875MG/15ML SC (containing 1,875 mg of atezolizumab and 30,000 units of hyaluronidase) administered subcutaneously in the thigh every 3 weeks (n = 247) or intravenous atezolizumab 1,200 mg every 3 weeks (n = 124) until disease progression or unacceptable toxicity.

The primary outcome measure was atezolizumab exposure (C_{trough} and $AUC_{0\text{-}21days}$) of subcutaneous TECENTRIQ 1875MG/15ML SC as compared to intravenous atezolizumab *[see Clinical Pharmacology (12.3)]*. Additional descriptive efficacy outcome measures were overall response rate (ORR), progression-free survival (PFS) and overall survival (OS).

The median age was 64 years (range: 27 to 85); 69% were male; 67% were White, 22% were Asian, and 0.8% were Black or African American; 74% were non-Hispanic or Latino; 26% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 74% had an ECOG PS of 1; and 70% of patients were current or previous smokers. Sixty-five percent of

patients had non-squamous histology, 5% had known EGFR mutations, 1.6% had known ALK rearrangements, 36% had known PD-L1 positive tumors, 16% had asymptomatic CNS metastases at baseline. Eighty percent of patients had received only one prior therapeutic regimen for NSCLC.

At the primary analysis, the confirmed ORR was 9% (95% CI: 5, 13) in the subcutaneous TECENTRIQ 1875MG/15ML SC arm and 8% (95% CI: 4, 14) in the intravenous atezolizumab arm. After further follow up, no notable differences in PFS and OS were observed between patients who received subcutaneous TECENTRIQ 1875MG/15ML SC and patients who received intravenous atezolizumab.

NSCLC Trials - Intravenous Atezolizumab

The effectiveness of TECENTRIQ 1875MG/15ML SC has been established for:

- adjuvant treatment (following tumor resection and platinum-based chemotherapy) in adult patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells (IMpower010 study).
- first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), with no EGFR or ALK genomic tumor aberrations (IMpower110 study).
- first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (IMpower150 study).
- first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (IMpower130 study).
- first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression, with no EGFR or ALK genomic tumor aberrations (OAK study).

Use of TECENTRIQ 1875MG/15ML SC for these NSCLC indications is supported by evidence from the adequate and well-controlled studies conducted with intravenous atezolizumab in these NSCLC populations and pharmacokinetics data that demonstrated comparable exposures to atezolizumab between TECENTRIQ 1875MG/15ML SC and intravenous atezolizumab in the IMscin001 trial *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. Below is a description of the efficacy results of these adequate and well-controlled studies of intravenous atezolizumab in these NSCLC populations.

Adjuvant Treatment of Early-stage NSCLC

IMpower010

The efficacy of intravenous atezolizumab was evaluated in IMpower010 (NCT02486718), a multi-center, randomized, open-label trial for the adjuvant treatment of patients with NSCLC who had complete tumor resection and were eligible to receive cisplatin-based adjuvant chemotherapy. Eligible patients were required to have Stage IB (tumors ≥ 4 cm) – Stage IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition. Patients were excluded if they had a history of autoimmune disease; a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis; administration of a live, attenuated vaccine within 28 days prior

to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

A total of 1005 patients who had complete tumor resection and received cisplatin-based adjuvant chemotherapy were randomized (1:1) to receive intravenous atezolizumab 1200 mg intravenous infusion every 3 weeks for 16 cycles, unless disease recurrence or unacceptable toxicity occurred, or best supportive care (BSC). Randomization was stratified by sex, stage of disease, histology, and PD-L1 expression.

Tumor assessments were conducted at baseline of the randomization phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%) and Asian (24%). Most patients were current or previous smokers (78%) and baseline Eastern Cooperative Oncology Group (ECOG) performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had Stage IB, 47% had Stage II and 41% had Stage IIIA disease. PD-L1 expression, defined as the percentage of tumor cells expressing PD-L1 as measured by the VENTANA PD-L1 (SP263) assay, was ≥ 1% in 53% of patients, <1% in 44% and unknown in 2.6%.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. The primary efficacy analysis population (n = 476) was patients with Stage II – IIIA NSCLC with PD-L1 expression on ≥ 1% of tumor cells (PD-L1 ≥ 1% TC). DFS was defined as the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. A key secondary efficacy outcome measure was overall survival (OS) in the intent-to-treat population.

At the time of the interim DFS analysis, the study demonstrated a statistically significant improvement in DFS in the PD-L1 ≥ 1% TC, Stage II – IIIA patient population.

Efficacy results are presented in Table 31 and Figure 2.

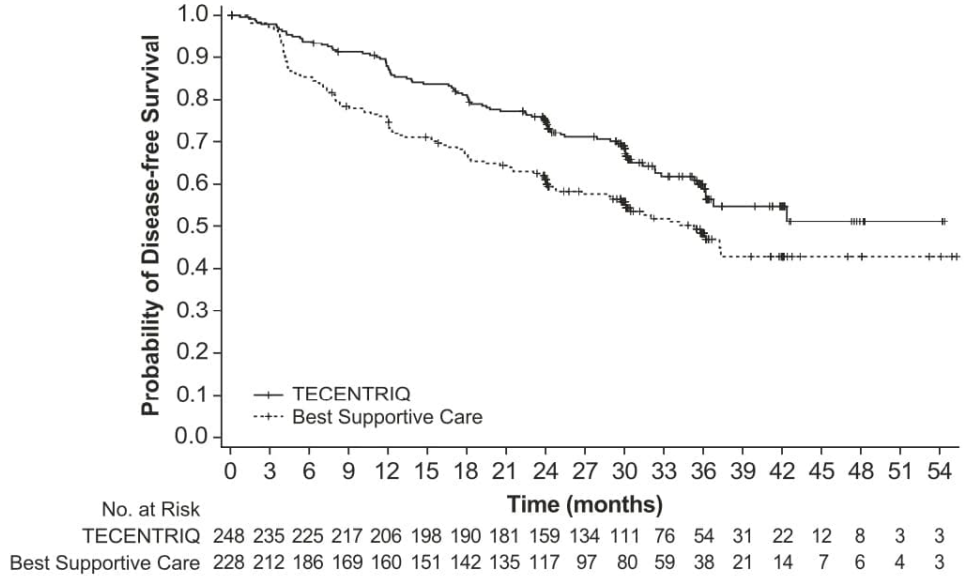
Table 31 Efficacy Results from IMpower010 in Patients with Stage II - IIIA NSCLC with PD-L1 expression ≥ 1% TC

	Arm A: Intravenous Atezolizumab N = 248	**Arm B: Best Supportive Care N = 228**
Disease-Free Survival		
Number of events (%)	88 (35)	105 (46)
Median, months	NR	35.3
(95% CI)	(36.1, NE)	(29.0, NE)
Hazard ratio[1] (95% CI)	0.66 (0.50, 0.88)	
p-value	0.004	

CI = Confidence interval, NE = Not estimable, NR = Not reached
[1] Stratified by stage, sex, and histology

In a pre-specified secondary subgroup analysis of patients with PD-L1 TC ≥ 50% Stage II – IIIA NSCLC (n=229), the median DFS was not reached (95% CI: 42.3 months, NE) for patients in the intravenous atezolizumab arm and was 35.7 months (95% CI: 29.7, NE) for patients in the best supportive care arm, with a HR of 0.43 (95% CI: 0.27, 0.68). In an exploratory subgroup analysis of patients with PD-L1 TC 1-49% Stage II – IIIA NSCLC (n=247), the median DFS was 32.8 months (95% CI: 29.4, NE) for patients in the intravenous atezolizumab arm and 31.4 months (95% CI: 24.0, NE) for patients in the best supportive care arm, with a HR of 0.87 (95% CI: 0.60, 1.26).

Figure 2: Kaplan-Meier Plot of Disease-Free Survival in IMpower010 in Patients with Stage II – IIIA NSCLC with PD-L1 expression ≥ 1% TC



At the time of the DFS interim analysis, 19% of patients in the PD-L1 ≥1% TC Stage II – IIIA patient population had died. An exploratory analysis of OS in this population resulted in a stratified HR of 0.77 (95% CI: 0.51, 1.17).

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

The efficacy of intravenous atezolizumab was evaluated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 1%]), who had received no prior chemotherapy for metastatic disease. PD-L1 tumor status was determined based on immunohistochemistry (IHC) testing using the VENTANA PD-L1 (SP142) Assay. The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%), excluding those with EGFR or ALK genomic tumor aberrations. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC vs. TC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms:

- Arm A: intravenous atezolizumab 1200 mg every 3 weeks until disease progression or unacceptable toxicity
- Arm B: Platinum-based chemotherapy

Arm B platinum-based chemotherapy regimens for non-squamous NSCLC consisted of cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) OR carboplatin (AUC 6 mg/mL/min) and pemetrexed (500 mg/m²) on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by pemetrexed 500 mg/m² until disease progression or unacceptable toxicity.

Arm B platinum-based chemotherapy regimens for squamous NSCLC consisted of cisplatin (75 mg/m²) on Day 1 with gemcitabine (1250 mg/m^2) on Days 1 and 8 of each 21-day cycle OR carboplatin (AUC 5 mg/mL/min) on Day 1 with gemcitabine (1000 mg/m^2) on Days 1 and 8 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care until disease progression or unacceptable toxicity.

Administration of intravenous atezolizumab was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses.

The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥50% or IC ≥10%; TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%.

Among the 205 chemotherapy-naïve patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC≥ 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease.

The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 32 and Figure 3.

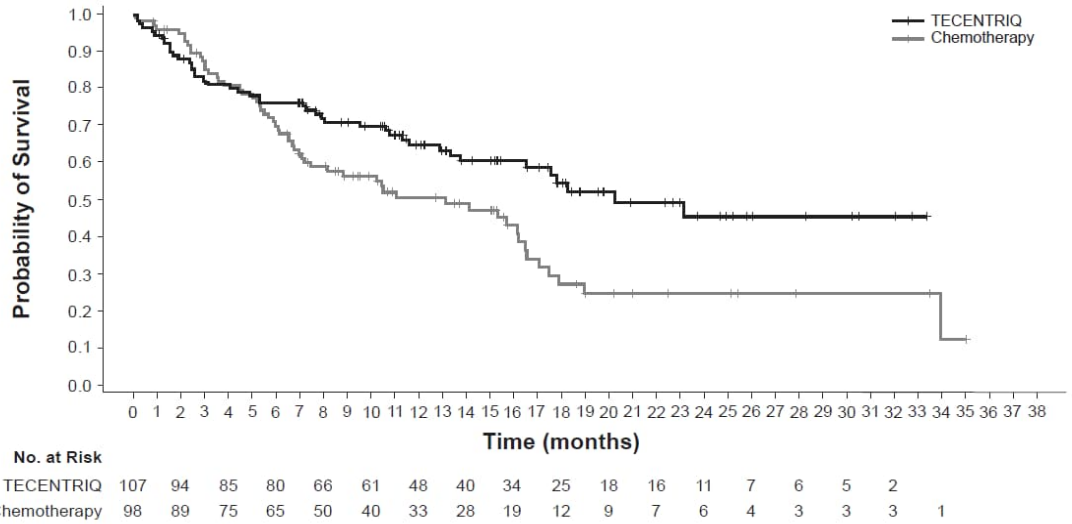
Table 32: Efficacy Results from IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations

	Arm A: Intravenous Atezolizumab N = 107	**Arm B: Platinum-Based Chemotherapy N = 98**
Overall Survival[1]		
Deaths (%)	44 (41%)	57 (58%)
Median, months	20.2	13.1
(95% CI)	(16.5, NE)	(7.4, 16.5)
Hazard ratio[2] (95% CI)	0.59 (0.40, 0.89)	

p-value[3]	0.0106[4]

[1] Based on OS interim analysis. The median survival follow-up time in patients was 15.7 months
[2] Stratified by sex and ECOG performance status
[3] Based on the stratified log-rank test compared to Arm A
[4] Compared to the allocated alpha of 0.0413 (two-sided) for this interim analysis
CI = confidence interval; NE = not estimable

Figure 3: Kaplan-Meier Plot of Overall Survival in IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and Without EGFR or ALK Genomic Tumor Aberrations



Investigator-assessed PFS showed an HR of 0.63 (95% CI: 0.45, 0.88), with median PFS of 8.1 months (95% CI: 6.8, 11.0) in the intravenous atezolizumab arm and 5 months (95% CI: 4.2, 5.7) in the platinum-based chemotherapy arm. The investigator-assessed confirmed ORR was 38% (95% CI: 29%, 48%) in the intravenous atezolizumab arm and 29% (95% CI: 20%, 39%) in the platinum-based chemotherapy arm.

First-Line Metastatic Non-Squamous NSCLC

IMpower150

The efficacy of intravenous atezolizumab with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in patients with metastatic non-squamous NSCLC. Patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE) status and ECOG performance status 0 or 1 were eligible. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging. Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms.

- Arm A: intravenous atezolizumab 1200 mg, paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: intravenous atezolizumab 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

Patients who had not experienced disease progression following the completion or cessation of platinum-based chemotherapy, received:

- Arm A: intravenous atezolizumab 1200 mg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm B: intravenous atezolizumab 1200 mg and bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm C: bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

Major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m^2 while the remaining 87% received paclitaxel at a dose of 200 mg/m^2. Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC.

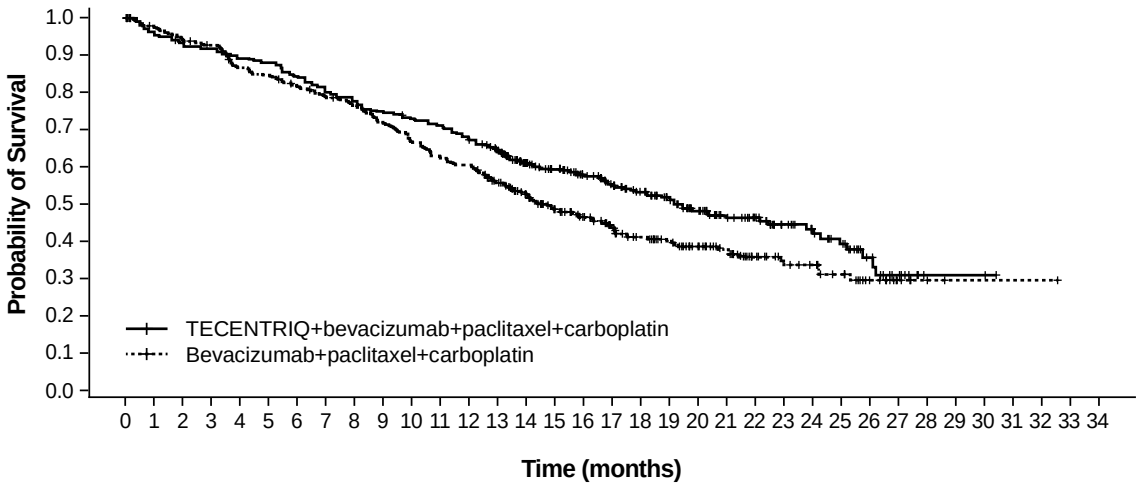
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 33 and Figure 4.

Table 33: Efficacy Results in ITT-WT Population in IMpower150

	Arm C: Bevacizumab, Paclitaxel and Carboplatin N = 337	Arm B: Intravenous Atezolizumab with Bevacizumab, Paclitaxel, and Carboplatin N = 359	Arm A: Intravenous Atezolizumab with Paclitaxel, and Carboplatin N = 349
Overall Survival[1]			
Deaths (%)	197 (59%)	179 (50%)	179 (51%)
Median, months	14.7	19.2	19.4
(95% CI)	(13.3, 16.9)	(17.0, 23.8)	(15.7, 21.3)
Hazard ratio[2] (95% CI)	---	0.78 (0.64, 0.96)	0.84 (0.72, 1.08)
p-value[3]	---	0.016[4]	0.204[5]
Progression-Free Survival[6]			
Number of events (%)	247 (73%)	247 (69%)	245 (70%)
Median, months	7.0	8.5	6.7
(95% CI)	(6.3, 7.9)	(7.3, 9.7)	(5.6, 6.9)
Hazard ratio[2] (95% CI)	---	0.71 (0.59, 0.85)	0.94 (0.79, 1.13)
p-value[3]	---	0.0002[7]	0.5219
Objective Response Rate[6]			
Number of responders (%)	142 (42%)	196 (55%)	150 (43%)
(95% CI)	(37, 48)	(49, 60)	(38, 48)
Complete Response	3 (1%)	14 (4%)	9 (3%)
Partial Response	139 (41%)	182 (51%)	141 (40%)
Duration of Response[6]	n = 142	n = 196	n = 150
Median, months	6.5	10.8	9.5
(95% CI)	(5.6, 7.6)	(8.4, 13.9)	(7.0, 13.0)

[1] Based on OS interim analysis
[2] Stratified by sex, presence of liver metastases, and PD-L1 expression status on TC and IC
[3] Based on the stratified log-rank test compared to Arm C
[4] Compared to the allocated α=0.0174 (two sided) for this interim analysis
[5] Compared to the allocated α=0.0128 (two sided) for this interim analysis
[6] As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7] Compared to the allocated α=0.006 (two sided) for the final PFS analysis
CI = confidence interval

Figure 4: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150



No. at Risk																													
TECENTRIQ+bevacizumab+paclitaxel+carboplatin	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bevacizumab+paclitaxel+carboplatin	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) *[see Clinical Pharmacology (12.6)]*. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the intravenous atezolizumab, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the intravenous atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

IMpower130

The efficacy of intravenous atezolizumab with paclitaxel protein-bound and carboplatin was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with stage IV non-squamous NSCLC. Patients with Stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor, if appropriate, were eligible. The trial excluded patients with history of autoimmune disease, administration of live attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Randomization was stratified by sex, presence of liver metastases, and PD-L1 tumor expression according to the VENTANA PD-L1 (SP142) assay as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following treatment regimens:

- Intravenous atezolizumab 1200 mg on Day 1, paclitaxel protein-bound 100 mg/m² on Days 1, 8, and 15, and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by intravenous atezolizumab 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- Paclitaxel protein-bound 100 mg/m² on Days 1, 8 and 15 and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care or pemetrexed.

Tumor assessments were conducted every 6 weeks for the first 48 weeks, then every 9 weeks thereafter. Major efficacy outcome measures were PFS by RECIST v1.1 and OS in the subpopulation of patients evaluated for and documented to have no EGFR or ALK genomic tumor aberrations (ITT-WT).

A total of 724 patients were enrolled; of these, 681 (94%) were in the ITT-WT population. The median age was 64 years (range: 18 to 86) and 59% were male. The majority of patients were White (90%), 2% of patients were Asian, 5% were Hispanic, and 4% were Black. Baseline ECOG performance status was 0 (41%) or 1 (58%). Most patients were current or previous smokers (90%). PD-L1 tumor expression was TC0/1/2 and IC0/1 in 73%; TC3 and any IC in 14%; and TC0/1/2 and IC2/3 in 13%.

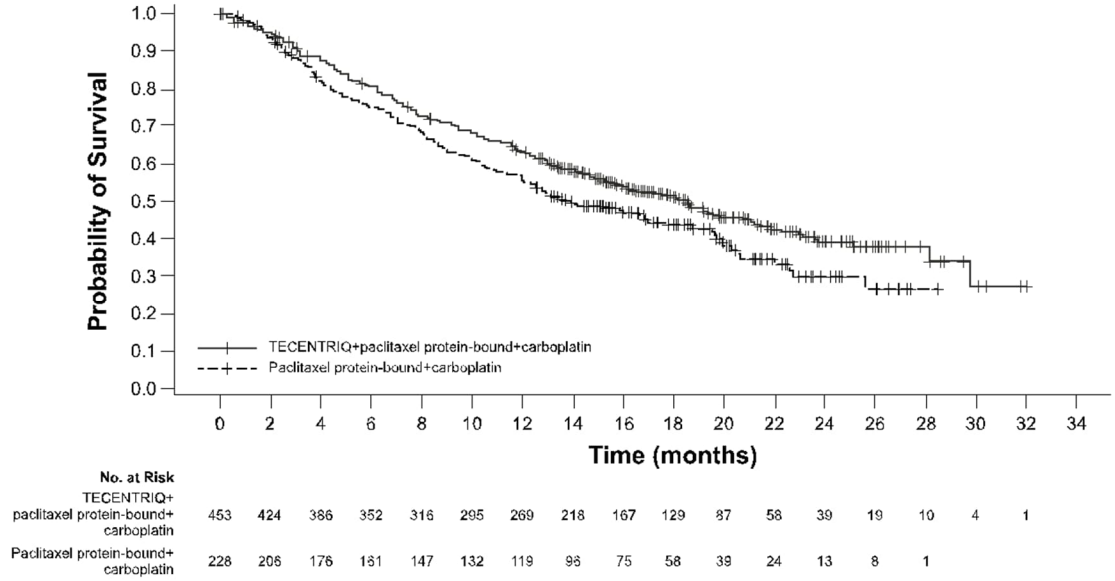
Efficacy results for the ITT-WT population are presented in Table 34 and Figure 5.

Table 34: Efficacy Results from IMpower130

	Intravenous Atezolizumab with Paclitaxel Protein-Bound and Carboplatin	**Paclitaxel Protein-Bound and Carboplatin**
Overall Survival[1]	n=453	n=228
Deaths (%)	228 (50%)	131 (57%)
Median, months	18.6	13.9
(95% CI)	(15.7, 21.1)	(12.0, 18.7)
Hazard ratio[2] (95% CI)	0.80 (0.64, 0.99)	
p-value[3]	0.0384[4]	
Progression-Free Survival[6]	n=453	n=228
Number of events (%)	330 (73%)	177 (78%)
Median, months	7.2	6.5
(95% CI)	(6.7, 8.3)	(5.6, 7.4)
Hazard ratio[2] (95% CI)	0.75 (0.63, 0.91)	
p-value[3]	0.0024[5]	
Overall Response Rate[6,7]	n=453	n=228
Number of responders (%)	207 (46%)	74 (32%)
(95% CI)	(41, 50)	(26, 39)
Complete Response	22 (5%)	2 (1%)
Partial Response	185 (41%)	72 (32%)
Duration of Response[6,7]	n=207	n=74
Median, months	10.8	7.8
(95% CI)	(9.0, 14.4)	(6.8, 10.9)

[1] Based on OS interim analysis
[2] Stratified by sex and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC)
[3] Based on the stratified log-rank test
[4] Compared to the allocated α=0.0428 (two sided) for this interim analysis
[5] Compared to the allocated α=0.006 (two sided) for the final PFS analysis
[6] As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7] Confirmed response
CI = confidence interval

Figure 5: Kaplan-Meier Curves for Overall Survival in IMpower130



Previously Treated Metastatic NSCLC

OAK

The efficacy of intravenous atezolizumab was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. non-squamous).

Patients were randomized to receive intravenous atezolizumab 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. Major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression,

overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1.

Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors.

Efficacy results are presented in Table 35 and Figure 6.

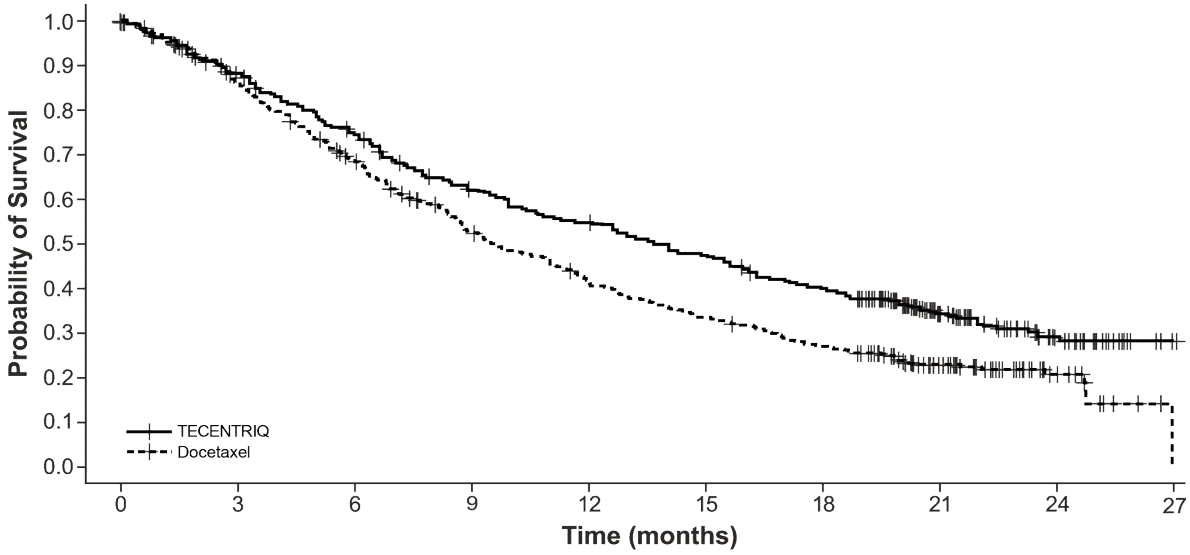
Table 35: Efficacy Results in OAK

	Intravenous Atezolizumab	**Docetaxel**
Overall Survival in first 850 patients		
Number of patients	N=425	N=425
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004[3]	
Progression-Free Survival		
Number of Patients	N=425	N=425
Events (%)	380 (89%)	375 (88%)
Progression (%)	332 (78%)	290 (68%)
Deaths (%)	48 (11%)	85 (20%)
Median, months	2.8	4.0
(95% CI)	(2.6, 3.0)	(3.3, 4.2)
Hazard ratio[1] (95% CI)	0.95 (0.82, 1.10)	
Overall Response Rate [4]		
Number of Patients	N=425	N=425
ORR, n (%)	58 (14%)	57 (13%)
(95% CI)	(11%, 17%)	(10%, 17%)
Complete Response	6 (1%)	1 (0.2%)
Partial Response	52 (12%)	56 (13%)
Duration of Response[3]	N=58	N=57
Median, months	16.3	6.2
(95% CI)	(10.0, NE)	(4.9, 7.6)
Overall Survival in all 1225 patients		
Number of patients	N=613	N=612
Deaths (%)	384 (63%)	409 (67%)
Median, months	13.3	9.8
(95% CI)	(11.3, 14.9)	(8.9, 11.3)

Hazard ratio[1] (95% CI)	0.79 (0.69, 0.91)
p-value[2]	0.0013[5]

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
[3] Compared to the pre-specified allocated α of 0.03 for this analysis
[4] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[5] Compared to the allocated α of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary
CI = confidence interval; NE = not estimable

Figure 6: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (79%) *[see Clinical Pharmacology (12.6)]*. ADA positive patients by week 4 appeared to have similar OS compared to docetaxel-treated patients. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the intravenous atezolizumab arm with a matched population in the docetaxel arm and ADA negative patients in the intravenous atezolizumab arm with a matched population in the docetaxel arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, histology (squamous vs. non-squamous), baseline albumin, baseline LDH, gender, tobacco history, metastases status (advanced or local), metastatic site, TC

level, and IC level. The hazard ratio comparing the ADA positive subgroup with its matched control was 0.89 (95% CI: 0.61, 1.3). The hazard ratio comparing the ADA negative subgroup with its matched control was 0.68 (95% CI: 0.55, 0.83).

14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

The efficacy of intravenous atezolizumab in combination with paclitaxel protein-bound was investigated in IMpassion130 (NCT02425891), a multicenter, international, double-blinded, placebo-controlled, randomized (1:1) trial that included 902 unresectable locally advanced or metastatic triple-negative breast cancer patients that had not received prior chemotherapy for metastatic disease. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 4 weeks prior to randomization, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases. Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC] <1% of tumor area vs. ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. Patients were randomized to receive intravenous atezolizumab 840 mg or placebo intravenously on Days 1 and 15 of every 28-day cycle with paclitaxel protein-bound 100 mg/m^2 intravenously on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Tumor assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter. Major efficacy outcomes were investigator-assessed progression free survival (PFS) (per RECIST v1.1) and overall survival (OS) in the ITT population and PD-L1 expressing patient population.

In IMpassion130, the median age was 55 years (range: 20-86). Overall, most patients were women (99.6%) and the majority of patients were white (68%), Asian (18%), Black or African American (7%), and American Indian or Alaskan Native (4.4%). The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Baseline ECOG performance status was 0 (58%) or 1 (41%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population.

Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses.

The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 36 and Figure 7.

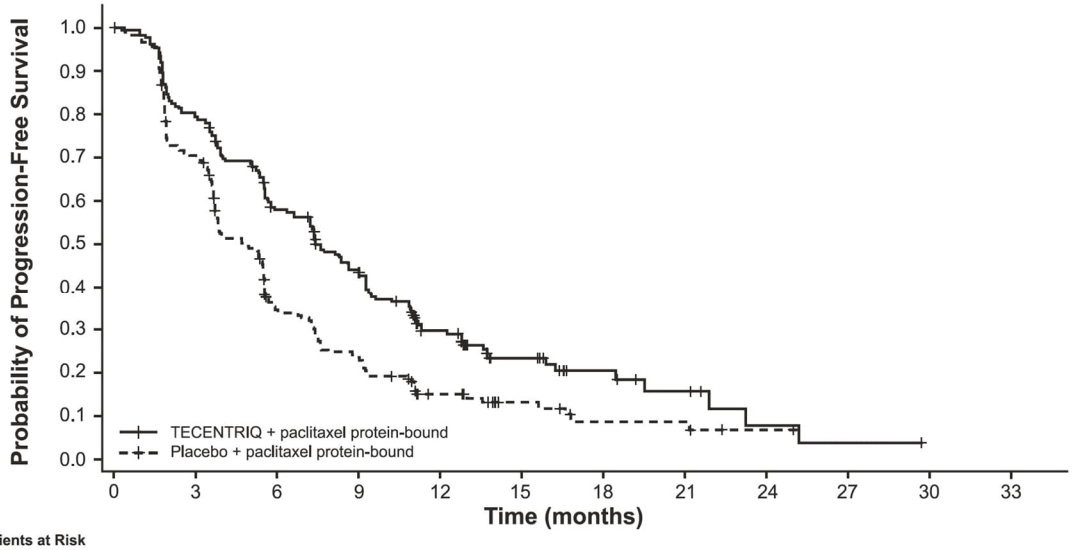
Table 36: Efficacy Results from IMpassion130 in Patients with PD-L1 Expression ≥ 1%

	PD-L1 Expression ≥ 1%[1]	
	Intravenous Atezolizumab in combination with paclitaxel protein-bound	**Placebo in combination with paclitaxel protein-bound**
Overall Survival[2]	n=185	n=184
Deaths (%)	120 (65%)	139 (76%)

Median, months (95% CI)	25.4 (19.6, 30.7)	17.9 (13.6, 20.3)
Hazard ratio (95% CI)	0.67 (0.53, 0.86)	
Progression-Free Survival [3,4]	(n=185)	(n=184)
Events (%)	136 (74)	151 (82)
Median, months (95% CI)	7.4 (6.6, 9.2)	4.8 (3.8, 5.5)
Stratified Hazard ratio (95% CI) [5]	0.60 (0.48, 0.77)	
p-value	<0.0001	
Objective Response Rate [3,4,6,7]	n=185	n=183
Number of responders (%)	98 (53)	60 (33)
(95% CI)	(45.5, 60.3)	(26.0, 40.1)
Complete Response (%)	17 (9)	1 (<1)
Partial Response (%)	81 (44)	59 (32)
Duration of Response [3,4,7]	n=98	n=60
Median, months	9.2	6.2
(95% CI)	(7.5, 11.9)	(5.5, 8.8)

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)
[2] OS in the PD-L1 expression ≥ 1% population was a major efficacy endpoint, but there remained no alpha to evaluate this endpoint. These results should be considered not statistically significant.
[3] As determined by investigator assessment
[4] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[5] Stratified by presence of liver metastases, and by prior taxane treatment
[6] Patients with measurable disease at baseline
[7] Confirmed responses
PFS=Progression-Free Survival; CI=Confidence Interval; ORR=Objective Response Rate; DOR=Duration of Response; NE=Not Estimable

Figure 7: Kaplan-Meier Plot of Progression-Free-Survival in IMpassion130 in Patients with PD-L1 Expression ≥1%



No. of Patients at Risk												
TECENTRIQ + paclitaxel protein-bound	185	145	102	73	38	19	10	6	2	1	NE	NE
Placebo + paclitaxel protein-bound	184	125	56	38	18	10	5	5	1	NE	NE	NE

14.4 Small Cell Lung Cancer

The efficacy of TECENTRIQ 1875MG/15ML SC in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) has been established in adequate and well-controlled studies of intravenous atezolizumab in combination with carboplatin and etoposide for ES-SCLC. Below is a description of the efficacy results of intravenous atezolizumab in combination with carboplatin and etoposide in this adequate and well-controlled ES-SCLC trial.

Small Cell Lung Cancer (SCLC)

IMpower133

The efficacy of intravenous atezolizumab with carboplatin and etoposide was investigated in IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC. IMpower133 enrolled patients with ES-SCLC who had received no prior chemotherapy for extensive stage disease and ECOG performance status 0 or 1. The trial excluded patients with active or untreated CNS metastases, history of autoimmune disease, administration of a live, attenuated vaccine within 4 weeks prior to randomization, or administration of systemic immunosuppressive medications within 1 week prior to randomization. Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. Patients were randomized to receive one of the following two treatment arms:

- Intravenous atezolizumab 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles followed by intravenous atezolizumab 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- placebo and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles followed by placebo once every 3 weeks until disease progression or unacceptable toxicity.

Administration of intravenous atezolizumab was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following

Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks until treatment discontinuation.

Major efficacy outcome measures were OS and PFS as assessed by investigator per RECIST v1.1 in the intent-to-treat population. Additional efficacy outcome measures included ORR and DoR as assessed by investigator per RECIST v1.1.

A total of 403 patients were randomized, including 201 to the intravenous atezolizumab arm and 202 to the chemotherapy alone arm. The median age was 64 years (range 26 to 90) and 65% were male. The majority of patients were White (80%); 17% were Asian, 4% were Hispanic and 1% were Black. Baseline ECOG performance status was 0 (35%) or 1 (65%); 9% of patients had a history of brain metastases, and 97% were current or previous smokers.

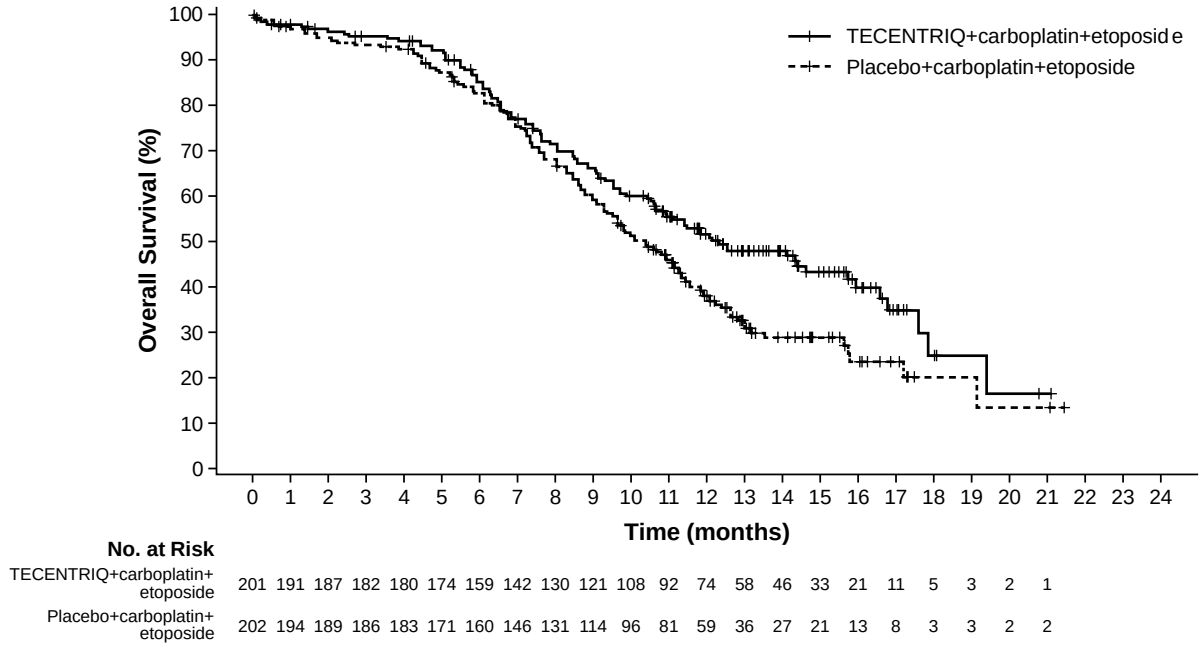
Efficacy results are presented in Table 37 and Figure 8.

Table 37: Efficacy Results from IMpower133

	Intravenous Atezolizumab with Carboplatin and Etoposide	**Placebo with Carboplatin and Etoposide**
Overall Survival	N=201	N=202
Deaths (%)	104 (52%)	134 (66%)
Median, months	12.3	10.3
(95% CI)	(10.8, 15.9)	(9.3, 11.3)
Hazard ratio[3] (95% CI)	0.70 (0.54, 0.91)	
p-value[4, 5]	0.0069	
Progression-Free Survival[1,2]	N=201	N=202
Number of events (%)	171 (85%)	189 (94%)
Median, months	5.2	4.3
(95% CI)	(4.4, 5.6)	(4.2, 4.5)
Hazard ratio[3] (95% CI)	0.77 (0.62, 0.96)	
p-value[4, 6]	0.0170	
Objective Response Rate[1,2,7]	N=201	N=202
Number of responders (%)	121 (60%)	130 (64%)
(95% CI)	(53, 67)	(57, 71)
Complete Response (%)	5 (2%)	2 (1%)
Partial Response (%)	116 (58%)	128 (63%)
Duration of Response[1,2,7]	N=121	N=130
Median, months	4.2	3.9
(95% CI)	(4.1, 4.5)	(3.1, 4.2)

[1] As determined by investigator assessment
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[3] Stratified by sex and ECOG performance status
[4] Based on the stratified log-rank test
[5] Compared to the allocated α of 0.0193 for this interim analysis based on 78% information using O'Brien-Fleming boundary
[6] Compared to the allocated α of 0.05 for this analysis
[7] Confirmed response
CI = confidence interval

Figure 8: Kaplan-Meier Plot of Overall Survival in IMpower133



14.5 Hepatocellular Carcinoma

The efficacy of TECENTRIQ 1875MG/15ML SC in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy has been established in adequate and well-controlled studies of intravenous atezolizumab in combination with bevacizumab for HCC. Below is a description of the efficacy results of intravenous atezolizumab in combination with bevacizumab in this adequate and well-controlled HCC trial.

Hepatocellular Carcinoma

IMbrave150

The efficacy of intravenous atezolizumab in combination with bevacizumab was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable and/or metastatic hepatocellular carcinoma who have not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL), and by ECOG performance status (0 vs. 1).

A total of 501 patients were randomized (2:1) to receive either intravenous atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg bevacizumab, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either intravenous atezolizumab or bevacizumab (e.g., due to adverse events) and continue on monotherapy until disease progression or unacceptable toxicity associated with the monotherapy.

The study enrolled patients who were ECOG performance score 0 or 1 and who had not received prior systemic treatment. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22%, and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B, and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per RECIST v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and mRECIST.

Efficacy results are presented in Table 38 and Figure 9.

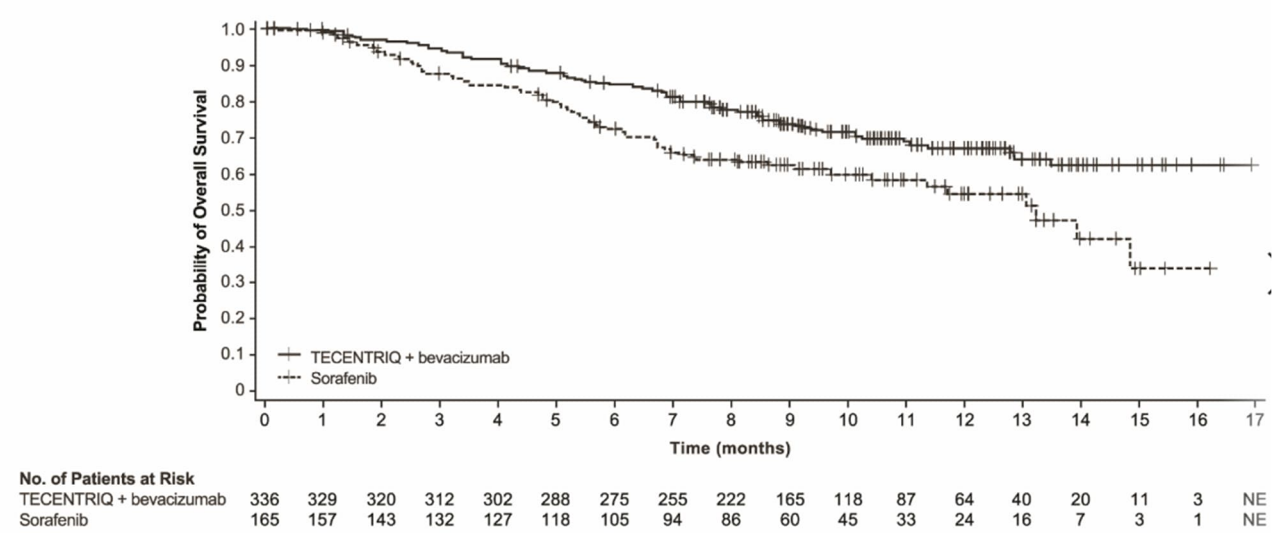
Table 38: Efficacy Results from IMbrave150

	Intravenous Atezolizumab in combination with Bevacizumab (N= 336)	**Sorafenib (N=165)**
Overall Survival		
Number of deaths (%)	96 (29)	65 (39)
Median OS in months (95% CI)	NE (NE, NE)	13.2 (10.4, NE)
Hazard ratio[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
Progression-Free Survival[3]		
Number of events(%)	197 (59)	109 (66)
Median PFS in months (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Hazard ratio[1] (95% CI)	0.59 (0.47, 0.76)	
p-value	<0.0001	
Overall Response Rate[3,5](ORR), RECIST 1.1		
Number of responders (%)	93 (28)	19 (12)
(95% CI)	(23, 33)	(7,17)
p-value[4]	<0.0001	
Complete responses, n (%)	22 (7)	0
Partial responses, n (%)	71 (21)	19 (12)
Duration of Response[3,5] (DOR) RECIST 1.1		
	(n=93)	(n=19)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.7, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)
Overall Response Rate[3,5] (ORR), HCC mRECIST		

Number of responders (%)	112 (33)	21 (13)
(95% CI)	(28, 39)	(8, 19)
p-value[4]	<0.0001	
Complete responses, n (%)	37 (11)	3 (1.8)
Partial responses, n (%)	75 (22)	18 (11)
Duration of Response[3,5] (DOR) HCC mRECIST		
	(n=112)	(n=21)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)

[1] Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (< 400 vs. ≥ 400 ng/mL)
[2] Based on two-sided stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on two-sided Cochran-Mantel-Haesnszel test
[5] Confirmed responses
+ Denotes a censored value
CI = confidence interval; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma; NE = not estimable; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors v1.1

Figure 9: Kaplan-Meier Plot of Overall Survival in IMbrave150



Exploratory analyses showed that the subset of patients (20%) who were ADA-positive by week 6 appeared to have reduced efficacy (effect on OS) as compared to patients (80%) who tested negative for treatment-emergent ADA by week 6 *[see Clinical Pharmacology (12.6)]*. ADA-positive patients by week 6 appeared to have similar overall survival compared to sorafenib-treated patients. In an exploratory analysis, inverse probability weighting was conducted to compare ADA-positive patients and ADA-negative patients in the intravenous atezolizumab and bevacizumab arm to the sorafenib arm. Inverse probability weighting factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, age, race, geographic region, weight, neutrophil-to-lymphocyte ratio, AFP (<400 ng/mL vs ≥400 ng/mL), number of metastatic sites, MVI and/or EHS present at study entry, etiology (HBV vs. HCV vs. non-viral) and Child-Pugh Score (A5 vs. A6). The OS hazard ratio comparing the ADA-positive subgroup of the intravenous atezolizumab and bevacizumab arm to sorafenib was 0.93 (95% CI:

0.57, 1.53). The OS hazard ratio comparing the ADA-negative subgroup to sorafenib was 0.39 (95% CI: 0.26, 0.60).

14.6 Melanoma

The efficacy of TECENTRIQ 1875MG/15ML SC in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma has been established in adequate and well-controlled studies of intravenous atezolizumab in combination with bevacizumab for BRAF V600 mutation-positive unresectable or metastatic melanoma. Below is a description of the efficacy results of intravenous atezolizumab in combination with cobimetinib and vemurafenib in this adequate and well-controlled melanoma trial.

Metastatic Melanoma

IMspire150

The efficacy of intravenous atezolizumab in combination with cobimetinib and vemurafenib was evaluated in a double-blind, randomized (1:1), placebo-controlled, multicenter trial (IMspire150; NCT02908672) conducted in 514 patients. Randomization was stratified by geographic location (North America vs. Europe vs. Australia, New Zealand, and others) and baseline lactate dehydrogenase (LDH) [less than or equal to upper limit of normal (ULN) vs. greater than ULN]. Eligible patients were required to have previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma as detected by a locally available test and centrally confirmed with the FoundationOne™ assay. Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; and active or untreated CNS metastases.

Intravenous atezolizumab was initiated after patients received a 28-day treatment cycle of cobimetinib 60 mg orally once daily (21 days on / 7 days off) and vemurafenib 960 mg orally twice daily Days 1-21 and 720 mg orally twice daily Days 22-28. Patients received intravenous atezolizumab 840 mg intravenous infusion over 60 minutes every 2 weeks in combination with cobimetinib 60 mg orally once daily and vemurafenib 720 mg orally twice daily, or placebo in combination with cobimetinib 60 mg orally once daily and vemurafenib 960 mg orally twice daily. Treatment continued until disease progression or unacceptable toxicity. There was no crossover at the time of disease progression. Tumor assessments were performed every 8 weeks (± 1 week) for the first 24 months and every 12 weeks (± 1 week) thereafter.

The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST v1.1. Additional efficacy outcomes included PFS assessed by an independent central review, investigator-assessed ORR, OS, and DOR.

The median age of the study population was 54 years (range: 22-88), 58% of patients were male, 95% were White, a baseline ECOG performance status of 0 (77%) or 1 (23%), 33% had elevated LDH, 94% had metastatic disease, 60% were Stage IV (M1C), 56% had less than three metastatic sites at baseline, 3% had prior treatment for brain metastases, 30% had liver metastases at baseline, and 14% had received prior adjuvant systemic therapy. Based on central

testing, 74% were identified as having a V600E mutation, 11% as having V600K mutation, and 1% as having V600D or V600R mutations.

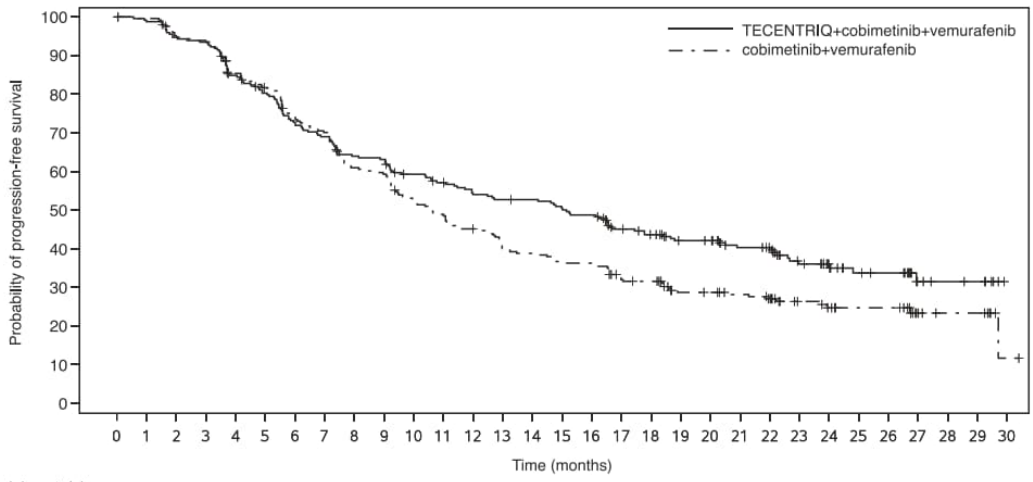
Efficacy results are summarized in Table 39 and Figure 10. Patients had a median survival follow up time of 18.9 months.

Table 39 Efficacy Results from IMspire150

	Intravenous Atezolizumab + Cobimetinib + Vemurafenib N=256	Placebo + Cobimetinib + Vemurafenib N=258
Progression-Free Survival[1]		
Number of events (%)	148 (58)	179 (69)
Median, months	15.1	10.6
(95% CI)	(11.4, 18.4)	(9.3, 12.7)
Hazard ratio[2] (95% CI)	0.78 (0.63, 0.97)	
p-value[3]	0.0249	
Overall Response Rate[1,4]		
Number of responders (%)	170 (66)	168 (65)
(95% CI)	(60, 72)	(59, 71)
Complete responses, n (%)	41 (16)	46 (18)
Partial response, n (%)	129 (50)	122 (47)
Duration of Response[1,4]	n=170	n=168
Median, months	20.4	12.5
(95% CI)	(15.1, NE)	(10.7, 16.6)

[1] As determined by investigator assessment with Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval;
[2] Stratified by baseline LDH
[3]Based on the stratified log-rank test
[4]Confirmed Responses

Figure 10: Kaplan-Meier Plot for Progression-Free Survival in IMspire150



At a pre-specified analysis at the time of the primary analysis of PFS, the OS data were not mature. The median OS was 28.8 months with 93 (36%) deaths in the intravenous atezolizumab plus cobimetinib and vemurafenib arm, and 25.1 months with 112 (43%) deaths in the placebo plus cobimetinib and vemurafenib arm. The hazard ratio for OS was 0.85 (95% CI: 0.64, 1.11) and the p-value was 0.2310.

14.7 Alveolar Soft Part Sarcoma

The efficacy of TECENTRIQ 1875MG/15ML SC as monotherapy for the treatment of adult patients with unresectable or metastatic alveolar soft part sarcoma (ASPS) has been established in adequate and well-controlled studies of intravenous atezolizumab for ASPS. TECENTRIQ 1875MG/15ML SC is not indicated for the treatment of pediatric patients. Below is a description of the efficacy results of intravenous atezolizumab in this adequate and well-controlled ASPS trial.

The efficacy of intravenous atezolizumab was evaluated in study ML39345 (NCT03141684), an open-label, single-arm study, in 49 adult and pediatric patients aged 2 years and older with unresectable or metastatic ASPS. Although this study enrolled pediatric patients, TECENTRIC SC is not indicated for use in pediatric patients. Eligible patients were required to have histologically or cytologically confirmed ASPS that was not curable by surgery, and an ECOG performance status of ≤ 2.

Patients were excluded if they had known primary central nervous system (CNS) malignancy or symptomatic CNS metastases, known clinically significant liver disease, or history of idiopathic pulmonary fibrosis, pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

Adult patients received 1200 mg intravenously and pediatric patients received 15 mg/kg (up to a maximum of 1200 mg) intravenously once every 21 days until disease progression or unacceptable toxicity.

The major efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DOR) by Independent Review Committee according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

A total of 49 patients were enrolled. The median age of patients was 31 years (range: 12-70); 2% of adult patients (n=47) were ≥65 years of age and the pediatric patients (n=2) were ≥12 years of age; 51% of patients were female, 55% White, 29% Black or African American, 10% Asian; 53% had an ECOG performance status of 0 and 45% had an ECOG performance status of 1. All patients had prior surgery for ASPS and 55% received at least one prior line of treatment for ASPS; 55% received radiotherapy and 53% received chemotherapy. Of the patients who reported staging at initial diagnosis, all were Stage IV.

Efficacy results of this study are summarized in Table 40.

Table 40: Efficacy Results from Study ML39345

Endpoint	All Patients (N=49)
Overall response rate (95% CI)[a]	24% (13, 39)
Complete Responses, n	0
Partial Responses, n (%)	12 (24)
Duration of response	
Median, month	NE
(95% CI)	(17.0, NE)
Range	1+, 41+
Durability of Response	
≥6 months, n (%)	8 (67%)
≥12 months, n (%)	5 (42%)

CI: confidence interval; N: number of patients; +: Censored

[a] 95% CI based on Clopper–Pearson exact method.

14.8 Patient Experience

The IMscin002 study was a randomized, multi-center, open-label cross-over trial conducted in 179 patients with either PD-L1-positive early-stage NSCLC receiving adjuvant treatment or were chemotherapy-naïve with high PD-L1 stage IV NSCLC. Patients were randomized (1:1) to receive 3 cycles of TECENTRIQ 1875MG/15ML SC followed by 3 cycles of intravenous atezolizumab (Arm A) or 3 cycles of intravenous atezolizumab followed by 3 cycles of TECENTRIQ 1875MG/15ML SC (Arm B).

Of the 126 eligible patients, 123 (98%) completed the patient preference questionnaire at the beginning of cycle 6 or after at least two consecutive cycles of each treatment method was administered in case of treatment discontinuation prior to cycle 6. Eighty-seven of 123 patients (71%) reported preferring subcutaneous administration of TECENTRIQ 1875MG/15ML SC over intravenous atezolizumab and the most common reason was that administration required less time in the clinic; 26 out of 123 patients (21%) reported preferring intravenous atezolizumab over TECENTRIQ 1875MG/15ML SC and the most common reason was that it felt more comfortable during administration; and 10 out of 123 patients (8%) had no preference for the route of administration.

Patients in both arms could continue to receive treatment after the crossover period for up to 16 cycles (patients with early-stage NSCLC) or until disease progression or unacceptable toxicity (patients with stage IV NSCLC). Of the 107 patients who reached the treatment continuation period, 85 (79%) patients (42 from IV/SC and 43 from SC/IV) chose to continue treatment with the SC route of administration.

16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ 1875MG/15ML SC (atezolizumab and hyaluronidase) injection for subcutaneous use is a sterile, preservative-free, clear, colorless to slightly yellowish liquid. It is supplied in a carton containing 1875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL) in a single-dose vial.

Store vials in a refrigerator at 2°C to 8°C in the outer carton in order to protect from light. Do not freeze. Do not shake.

Shelf-life

Unopened vial
The expiry date of the product is indicated on the packaging materials.

Prepared syringe

Once transferred from the vial into the syringe, TECENTRIQ 1875MG/15ML SC solution for injection is physically and chemically stable for up to 30 days at 2 °C to 8 °C and for up to 8 hours at ≤ 30 °C in diffuse daylight and from the time of preparation.

From a microbiological point of view, the solution should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place under controlled and validated aseptic conditions.

17 MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

18 MARKETING AUTHORISATION NUMBER(S):

180-57-38045-00

19 MANUFACTURER

F. Hoffmann-La Roche ltd, Basel, Switzerland

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